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Role of the normal female urethra in the sphincter mechanism of the bladder

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IF ONE asks where the focal point of bladder control is, what constitutes this mechanism, and how it functions, an accurate answer is not available and opinion will vary considerably.

The gynecologist's understanding of the anatomy, physiology, and pathology of the bladder is generally incomplete in spite of frequent involvement in many obstetric and gynecologic problems. The empiric anterior repair for cystocele is easily justified by the satisfactory anatomic and symptomatic results However, all leading workers have experienced failure, particularly with severe problems in the management of anatomic urinary incontinence.

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This involves a specific function of the bladder and as such deserves a reasonable understanding of bladder control. Much has been done in the anatomy of the bladder and physiology of micturition; however, the mechanism of bladder continence has received limited attention and is poorly understood. This is surprising in view of the efficiency of the system: a continent individual maintains a watertight seal in a dependent part of the bladder, containing up to 500 c.c. of fluid, with a resting pressure of 15 to 25 mm. Hg, and frequent momentary increases to 50 or 60 mm. Hg associated with increased intra-abdominal pressure.

Present study

Many statements made in regard to bladder control are the result of observations from studies of incontinence. This can be a useful method of investigation. However,

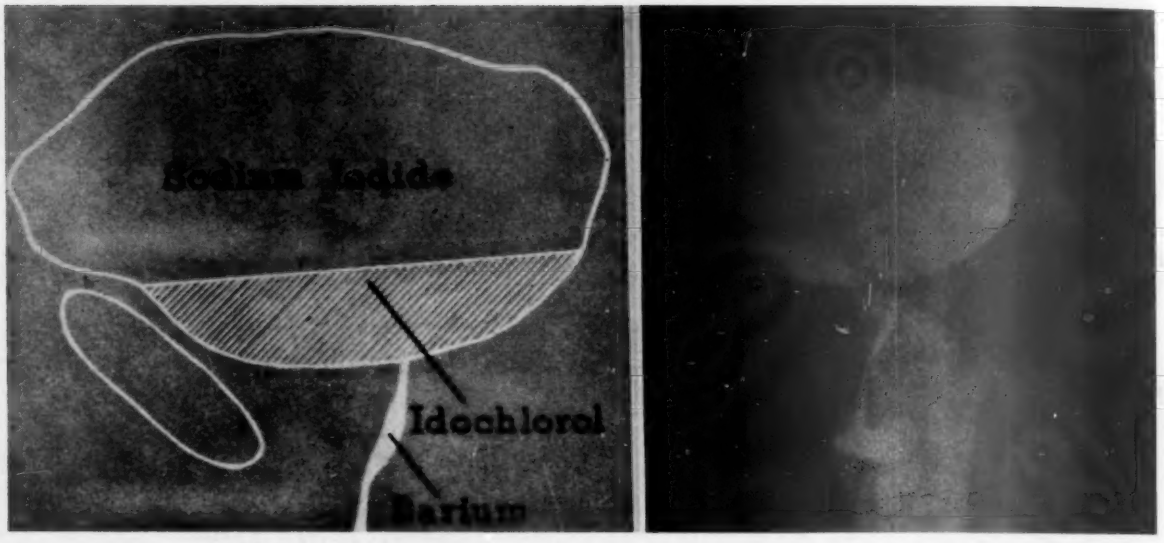

Fig. 1. Technique of cystourethrography

in view of our present hazy knowledge of this mechanism, it may just as easily direct our attention away from points of primary importance.

The present investigation is an effort to define the characteristics of the normal urethra and bladder, with the sphincter mechanism functioning to maintain continence, that is, with the patient at rest with a partially filled bladder, and, from these observations, to focus our attention on the site of bladder continence and to put forward a few hypotheses as to how this mechanism may function.

Forty-five volunteers with good bladder control have been studied. A number of groups were considered in view of the potential significance of age and parity.

A technique of cystourethrography (Fig. 1) has been devised in an attempt to reduce distortion of anatomic detail to a minimum. The bladder is filled with 200 c.c. of 5 per cent Na iodide and 20 c.c. of Iodochloral, the latter to define more clearly the bladder floor. The definition of the urethra is accomplished by the injection of a thin barium paste into the urethra during the gradual withdrawal of a small urethral catheter. This adheres to the urethral mucosa in a manner similar to the postevacuation film of a barium enema. A sterile technique is used throughout this procedure and, except for occasional brief periods of urethral irritability characteristic of catheterization, there have been no complications.

A standard series of 4 films, an anteroposterior and 3 standing lateral views, are taken. The anteroposterior and the first standing lateral film show the patient at rest. The second film is taken with the patient voluntarily holding, that is, striving to augment this mechanism. The third film is

Fig. 2. Composite picture of the normal bladder and urethra.

taken with the patient straining when the increased intra-abdominal pressure will bring the greatest stress to bear upon the sphincter mechanism.

It has been suggested that the injected barium will distort the anatomic detail of the urethra. The injection is done with a soft rubber catheter and we have found that as the catheter is withdrawn from the bladder into the urethra during injection, the tone of the urethral wall forces the catheter out as the lumen is filled. This results in a certain uniformity of technique and acts in effect as a measure of the tone of the urethral musculature. Therefore, although distortion may occur, it will not be a serious problem if a consistent method of injection and consistency of barium is used. A number of opportunities have arisen to repeat films and in general the detail of the urethra has been identical in successive studies.

Results

Composite of total series. Fig. 2 is a composite picture of 45 cases studied.

The posterior bladder floor is flat and 3.5 cm. in length. The anterior bladder floor is short and may be flat or demonstrate a small hump immediately in front of the urethra.

The bladder neck is situated behind and above the level of the inferior border of the symphysis in the standing position. The bladder neck is sharply defined in relation to the bladder floor with a characteristically narrow lumen, 1.0 mm. in diameter, which is continuous with a constriction 1.0 cm. in length and 1.0 mm. in diameter involving the upper one third of the urethra. The posterior urethrovesical angle between the posterior bladder floor and the upper one third of the urethra is 125 degrees.

The middle third of the urethra is characterized by a moderate fullness measuring 3.0 mm. in diameter, while the lower third contains a second constriction. The urethra is 4.7 cm. in length and demonstrates a gentle forward curve in its downward course from the bladder neck.

The variations of the urethra, bladder neck, and bladder floor which contribute to this composite will be considered briefly.

Anatomic features

Position of the bladder neck. The position of the bladder neck in the pelvis is related to the inferior border of the symphysis, and a base line is drawn through the midpoint

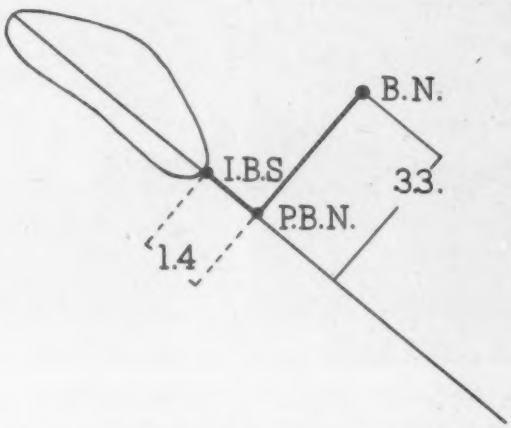

Fig. 3. Average position of normal bladder neck. B.N., bladder neck; P.B.N., perpendicular to bladder neck; I.B.S., inferior border of symphysis pubis.

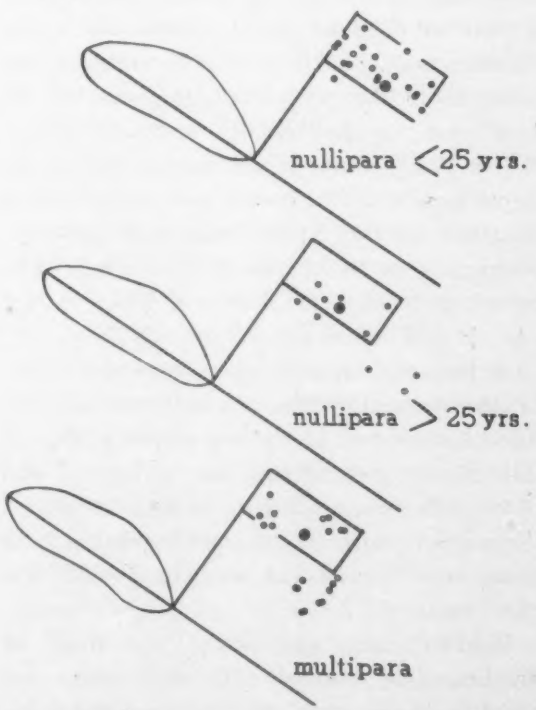

Fig. 4. Range of position of normal bladder neck; ○one patient, ● average position of bladder neck.

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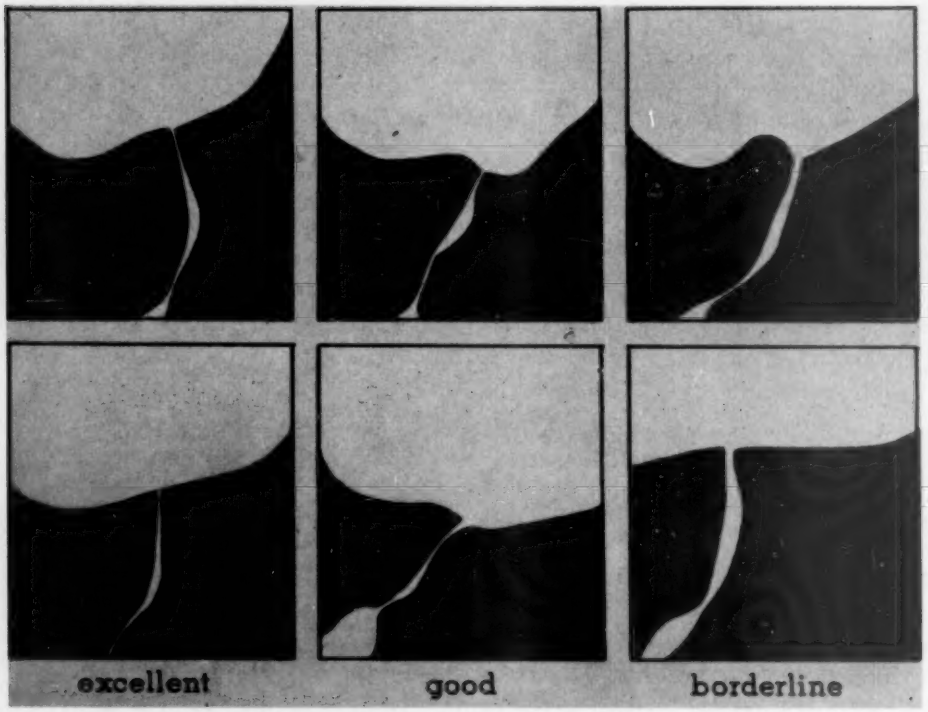

Fig. 5. Normal variations in bladder neck and upper one third of urethra.

of the superior and inferior border of the symphysis (Fig. 3). The position is documented by two observations, the distance from the inferior border of the symphysis to a point on the base line perpendicular to the bladder neck (I.B.S—P.B.N.), and the distance from the perpendicular point on the base line to the bladder neck (P.B.N.—B.N.). An increase in the former represents downward and backward movement and a decrease of the latter downward and forward movement of the bladder neck. The mean position was: I.B.S—P.B.N. = 1.4 cm.; P.B.N.—B.N. = 3.3 cm.

A limited range of position was evident in the young nulliparous patients as outlined by the box in the top panel of Fig. 4. There was a tendency for a few of the older nulliparous patients to demonstrate a downward and forward and the multiparous patients a downward and backward displacement.

Bladder neck and upper one third of urethra. The bladder neck and upper one third of the urethra are best considered together because of the obvious close functional relationship (Fig. 5). The characteristic of these continent patients is a narrow, clearly defined bladder neck with a 1.0 mm. lumen which is continuous with a constriction involving the upper one third of the urethra, 1.0 cm. in length, and again with a lumen 1.0 mm. in diameter as demonstrated in the left and center panels. There were 7 cases demonstrating some variation from this pattern with a 2 to 3 mm. widening of the lumen of the bladder neck and upper one third of the urethra. This latter group of borderline anatomic variants occurred in nulliparous patients, 4 less than and 3 over 25 years of age.

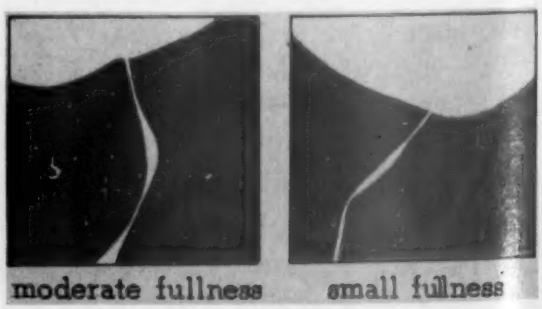

Fig. 6. Middle and lower one third of urethra.

These observations would imply an efficient muscle system in the wall of the urethra in order to maintain this narrow lumen at the bladder neck and throughout the length of the upper one third of the urethra.

Middle and lower one third of urethra. The remainder of the urethra falls logically into two segments (Fig. 6), a middle one third extending from the constriction of the upper one third to the level of the urogenital diaphragm, and a lower one third passing through the urogenital diaphragm to open into the ampulla of the external meatus.

The middle one third of the urethra is characterized by a fullness which easily distinguishes it from the constriction of the upper and lower one third. There were two distinct types. A moderate fullness measuring 3 or 4 mm. in diameter was noted in 26 cases, while a small fullness 1 or 2 mm. in diameter was observed in 19 cases.

The lower one third of the urethra is characterized by a second constriction which opens into the ampulla of the external meatus. This was a long constriction in 25 cases and a moderate constriction in 20 cases.

The middle one third of the urethra situated above the urogenital diaphragm has its own intrinsic musculature within the urethral wall but no additional extrinsic support. The lower one third of the urethra is situated within the urogenital diaphragm and, in addition to the intrinsic musculature, it is supported by a very significant layer of encircling striated muscle fibers arising from the pubococcygeus and vagina. This provides a reasonable explanation for the fullness of the middle one third and the second constriction in the lower one third of the urethra.

Total urethra. The average length of the total urethra was 4.7 cm., with the majority of cases between 4.5 to 5.0 cm.

The urethra has a slight forward curve in its downward course from the bladder neck. This was given a shallow S-shaped appearance in 18 cases because of a downward and backward rotation of the urethra as it passed through the urogenital diaphragm.

Posterior bladder floor. Two types of posterior bladder floor were observed (Fig. 7). A straight posterior floor was found in two thirds (29) of the cases. The average length was 3.7 cm. with a range from 1.0 to 6.0 cm. Second, a slightly curved floor, in one third (16 cases), in which a gentle curve begins from the urethra and flows into the posterior bladder wall. The length of the curving posterior floor is not so easily defined as the distinction between the bladder floor and posterior bladder wall is not as clear cut. However, the apparently relevant posterior floor was somewhat shorter with an average length of 2.3 cm. and a range from 1.0 to 4.0 cm.

Anterior bladder floor. Two types of anterior bladder floor were observed (Fig. 8). A short straight anterior bladder floor was seen in one third (16) of the cases. The remaining two thirds (29 cases) demonstrated a distinct hump immediately in front of the urethra. This hump was slight or small in 18 and moderate or large in 11 cases.

The significance of this hump cannot be reasonably defined in the absence of an adequate anatomic explanation. However, an appreciation of its occurrence is necessary for radiologic evaluation because this humping, particularly if marked, can create a misleading impression of funneling of the bladder neck on casual observation.

Lateral bladder floor. The common pattern of the lateral bladder floor is a gentle curve to an angle of 25 degrees with the horizontal observed in 35 cases (Fig. 9). Individual variation is demonstrated in a number of ways. The two sides are symmetrical in only half the cases. The curvature of the floor is fairly uniform in two thirds, but somewhat irregular in the remainder.

The lateral floor is flat and straight immediately adjacent to the urethra for a distance of 1.0 cm. in a small number (10) of cases with a somewhat more oblique curve (average 32 degrees) beyond this point. This picture was more commonly observed in the young nulliparous patient.

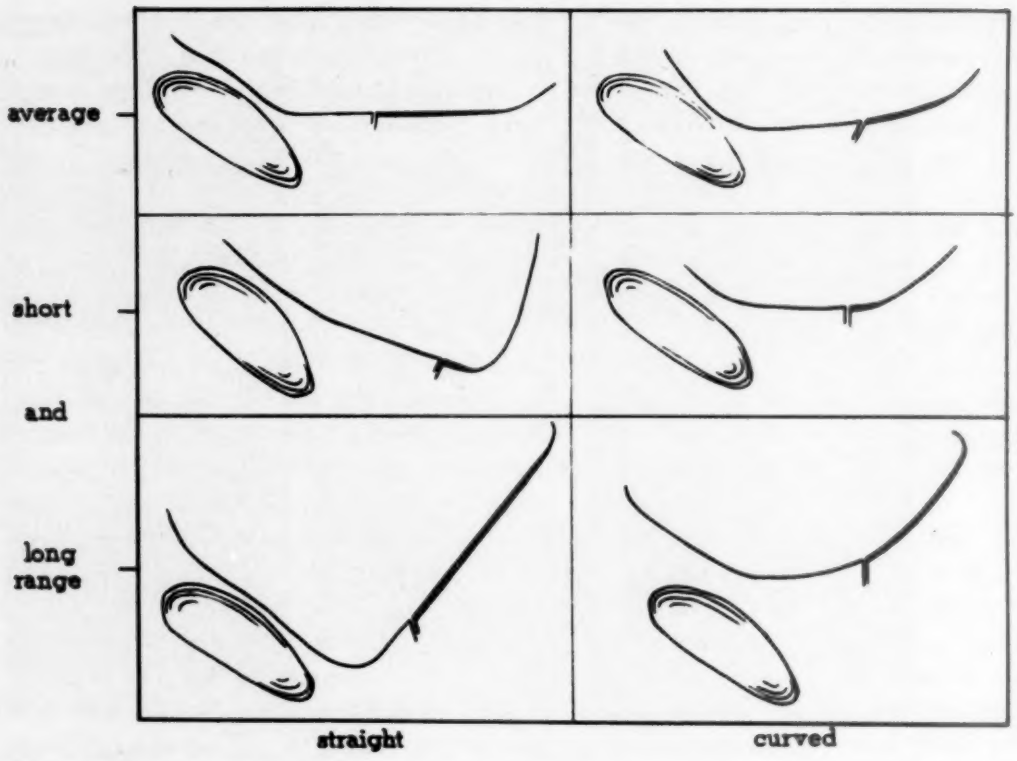

Fig. 7. Posterior bladder floor.

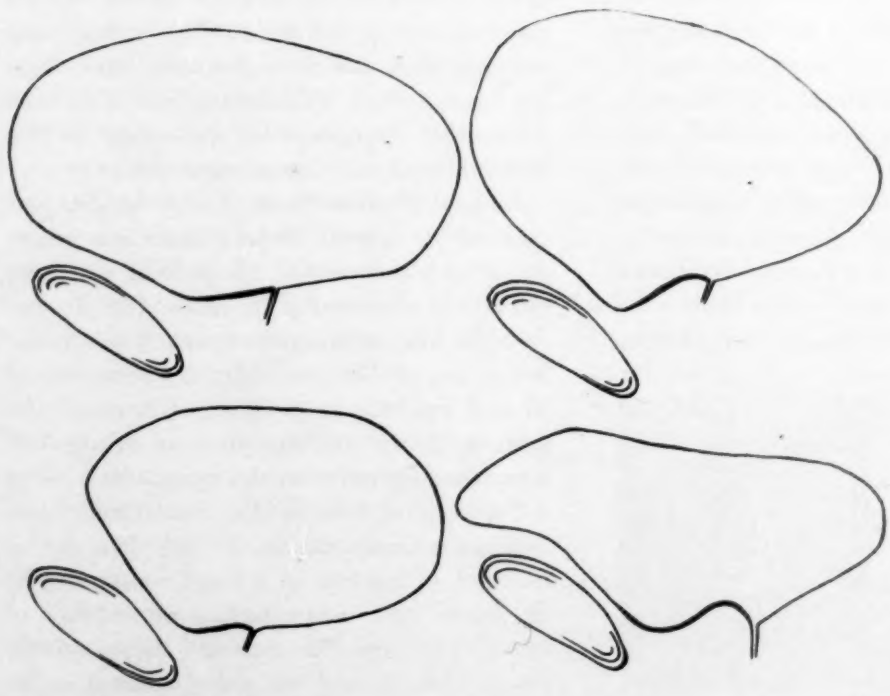

Fig. 8. Anterior bladder floor.

Posterior urethrovesical angle. Recent clinical studies[1-4] have extensively explored the empirical posterior urethrovesical angle (Fig. 10).

The average posterior urethrovesical angle in this series was 125 degrees with a range from 110 to 135 degrees in young nulliparous patients. The older and parous patients demonstrated a greater range from 90 to 160 degrees. The variations of the posterior angle are not influenced by the type or angle of the posterior floor or the position of the bladder neck.

Comment

It is evident that in a series of normal patients there is a certain range in the measurements of the anatomic features studied. These variations are essentially individual characteristics. The parous and older patients demonstrate a tendency to displacement of the bladder neck and a greater range of the posterior urethrovesical angle, but fewer variants of the bladder neck and urethra.

When one considers the mechanism of bladder continence, the first important problem is to define the site of this function. The present vagueness of concepts is due largely to the lack of an easily defined anatomic sphincter mechanism.

The cystourethrogram (Fig. 11) in the right panel demonstrates the outline of the normal bladder and urethra of a continent patient at rest. When the patient voids, the urethra opens and the bladder empties.

The cystogram in the left panel, again taken at rest, demonstrates the outline of the same moderately filled bladder. The bladder floor is smooth, giving no indication of the site of the bladder neck and urethra.

It is apparent that fluid comes to the bladder neck but does not enter the urethra. Thus, it seems obvious that the immediate bladder neck and upper one third of the urethra must represent the critical first line of defense with possibly the total urethra playing a role.

When one considers a functional mechanism which would produce the anatomic characteristics observed, it is well to recall that there are certain inherent dangers in an attempt to define function from a study of anatomic detail which represents the

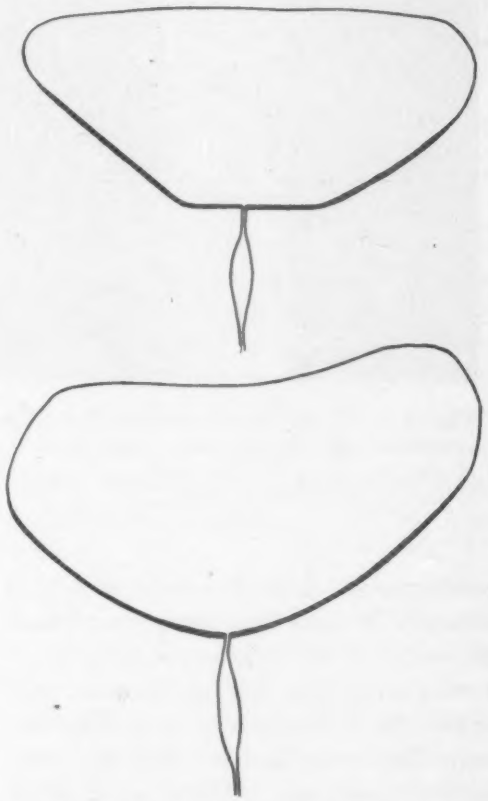

Fig. 9. Lateral bladder floor.

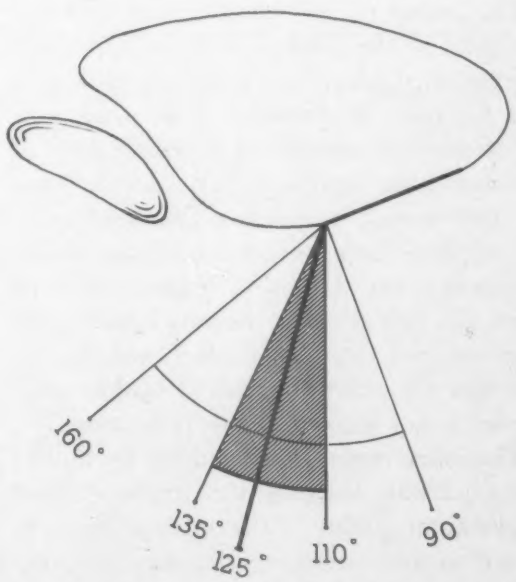

Fig. 10. Posterior urethrovesical angle.

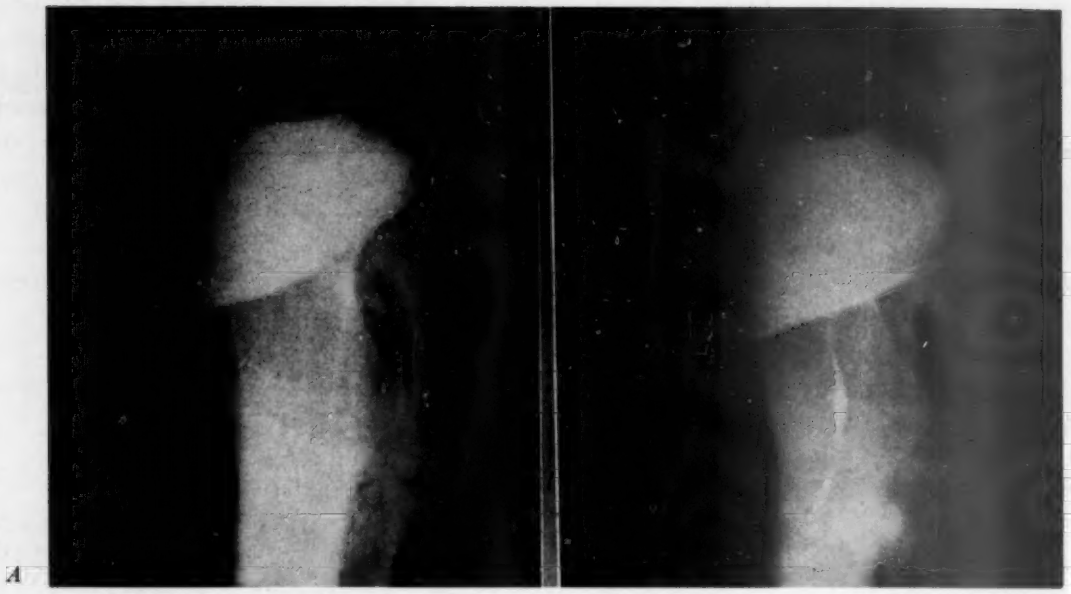

Fig. 11. The *(A)* cystogram and *(B)* cystourethrogram are taken at rest. It is evident in the cystogram that fluid comes to but does not enter the urethra, emphasizing the importance of the immediate bladder neck and upper one third of the urethra as the first line of defense of the sphincter mechanism.

characteristics of a single phase, and final confirmation of such hypotheses requires a specific study of the function itself.

However, accepting that the bladder neck and upper one third of the urethra (Fig. 12) represent the first line of defense, it is reasonable to assume that this segment of the urethra plays a major role in the mechanism of bladder control.

The lumen of the bladder neck and upper third of the urethra is characteristically an elongated constriction, 1.0 cm. in length and 1.0 mm. in diameter. This would imply a urethral wall of good muscle tone to maintain this narrow lumen and, in conjunction with a vascular submucosal cushion, suggests an effective collar-like sphincter mechanism. However, slight variations from this characteristic narrow lumen were observed in a few cases which would suggest that the entire function of bladder continence is not focused at this point alone.

The occurrence of variations in nulliparous patients suggests the importance of the inherent quality of the original tissues in regard to their functional capacity and may well account for the incontinence seen in young patients during pregnancy and the severe incontinence occasionally observed in the older nulliparous patient.

Lapides[5] has expounded the concept of a sphincter mechanism based upon "the total resistance" of the muscular wall of the full

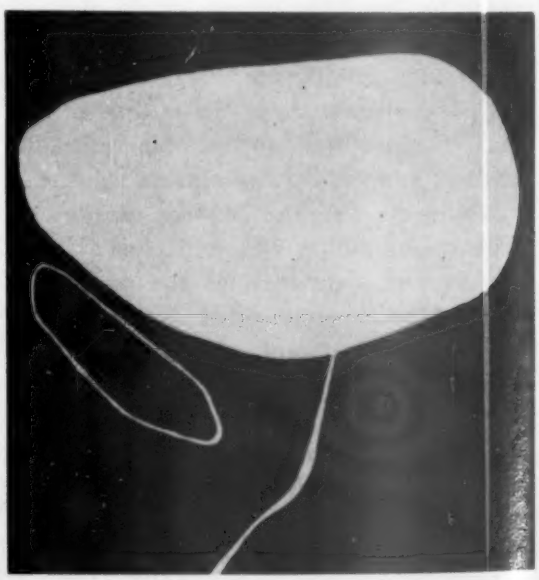

Fig. 12. Factors relevant to sphincter function. 1, Bladder neck and upper one third of urethra; 2, total urethra; 3, posterior urethrovesical angle; 4, bladder floor.

length of the urethra and has supported this hypothesis with some very interesting work in dogs, producing a continent bladder by an artificial urethra of bladder wall of sufficient length. This concept would seem quite compatible with the present observations, the lower two thirds, and particularly the lower third, of the urethra provided additional muscular tone to add to the resistance of the upper third of the urethra and bladder neck.

The posterior urethrovesical angle was 125 degrees, with a range from 90 to 160 degrees. This has been an empirical observation and its significance is not clear. However, with rare exception, an angle of 140 degrees or less is observed in continent individuals, the angle is lost in incontinence, and re-establishing the angle by surgical technique results in improved bladder control. Therefore, it would seem to be of some relevance to the function of the sphincter mechanism. There is an element of muscular continuity between the trigone, posterior bladder floor, and upper third of the urethra, and it may be that a good posterior angle is conducive to effective function of this muscle layer.

The possible significance of the type of bladder floor has not received serious attention. It may be that the individual with a large, flat bladder floor and a good posterior angle has a broad surface over which increased intravesical pressure can be diffused, particularly while standing, whereas, in the absence of an effective bladder floor and with loss of the posterior angle, the bladder neck is in the most dependent part of the bladder and the total effect of any increase of intravesical pressure is brought to bear directly upon the immediate bladder neck.

Summary

A method of cystourethrography to study the anatomic detail of the bladder, bladder neck, and urethra has been presented and the observations from a normal series of 45 patients described. A composite picture and the variants of the anatomic features have been discussed. The limited effect of age and parity in the otherwise continent individual upon anatomic detail has been observed.

The concept of bladder continence as a function of the urethra, with the bladder neck and upper one third of the urethra as the critical first line of defense, has been discussed, and the possible significance of the immediate bladder neck and upper one third of the urethra, the total urethra, the posterior urethrovesical angle, and the bladder floor have been considered.

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Therapeutic abortion in the Winnipeg General Hospital

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THE subject of therapeutic abortion always has been, and still is, one of the most controversial in medical practice. Opinions range from the belief that therapeutic abortion is never justifiable under any circumstances to the opinion, just as firmly held, that it should be performed almost upon demand by the patient. So many moral, ethical, religious and socioeconomic principles are involved that, at times, the purely medical aspect tends to be overlooked. Even the legal aspects of therapeutic abortion are not well defined but, as a rule, where the abortion has been performed openly, in hospital, after due consultation and "for the purpose of preserving the life of the mother" no legal action will be taken. The celebrated case in England of Alec Bourne gave legal sanction to the view that "for the purpose of preserving the life of the mother" included her emotional life as well as her physical life. The legal viewpoint will not be discussed further in this paper.

The use of the word "therapeutic" implies that some condition has been treated by the performance of the abortion, but only very rarely is this the case. Pregnancy when uncomplicated by a disease process is a normal state. However, pregnancy does alter the maternal metabolism and does make extra demands on the forces of the mother—therefore it has long been the view that if the patient is suffering already from some illness or disease, the addition of pregnancy will affect this disease process adversely with the result that the mother's life may be in jeopardy. In the past, as medical science often was unable to alter the course of the disease process, the obvious answer seemed to be to remove the pregnancy and thereby abolish the added strain to the patient. More recently, except in the case of conditions such as hypertensive and renal diseases which have a direct influence on the physiology of pregnancy, this argument has been shown to be illogical. There are very few conditions which have an adverse effect on or are unfavorably influenced by pregnancy if the appropriate management of both the disease and the pregnancy is carried out conscientiously by the patient and physician. Also, as new advances are made in the treatment of disease, more than ever it becomes possible to remove the threat to the life of the pregnant patient by the correct management of the disease and allowing the pregnancy to continue rather than by removing the pregnancy. Thus, the number of conditions in which it is necessary to remove the pregnancy to preserve the life of the mother is diminishing constantly so that today it should only be in very rare circumstances that therapeutic abortion is required.

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Material and incidence

All therapeutic abortions performed in the Winnipeg General Hospital during the

years 1953 to 1959 have been reviewed. During these 7 years 77 therapeutic abortions were performed, an average of 11 per year. During this same period of time there were 28,762 deliveries in the hospital—thus the ratio of therapeutic abortions to deliveries was 1 to 373. This compares very favorably with other reported series. Tietze[12] reported an incidence in New York City of 1 to 213, Loth and Hesseltine[7] 1 to 191 in Chicago, and Scherman[11] 1 to 227 in Portland, Oregon. However, extremes of 1 to 76 have been reported by Perlmutter[9] and 1 to 16,750 by Cosgrove and Carter.[2] Heffernan and Lynch[6] estimate that over 18,000 therapeutic abortions are performed annually in the United States and, from 152 replies to a questionnaire sent to 367 hospitals, they established the interesting fact that the maternal death rates in those hospitals where therapeutic abortions were performed, while excellent, were not better than those in the hospitals in which no therapeutic abortions were allowed.

Parity

Six (8 per cent) of the patients were nulliparous, although one of these with hypertensive disease had had 10 unsuccessful pregnancies. This is a low percentage of nulliparous patients—in contrast to Scherman's[11] series in which 17 per cent were nulliparous.

Age

Table 1 shows the age distribution. The youngest, a child who had been raped, was 13 years and the oldest, a patient with breast carcinoma, was 44 years.

Indications for therapeutic abortion

The indications are as listed in Table II.

Psychiatric disease

Twenty-seven cases (35.1 per cent) had a therapeutic abortion for psychiatric reasons and, as in most reported series, this is the most common indication. Two of these cases had also had a previous pregnancy terminated for psychiatric reasons.

Table I. Age distribution in 77 cases of therapeutic abortion

Age	*No. cases*
13	1
22-25	13
26-30	18
31-35	18
36-40	22
41-44	5
Total	77

Table II. Indications for 77 cases of therapeutic abortion

	No. cases	*Per cent*
Psychiatric disease	27	35.1
Neurological disease	8	10.4
Hypertensive disease	10	13.0
Heart disease	8	10.4
Renal disease	4	5.2
Previous carcinoma	4	5.2
Fetal indications	4	5.2
Miscellaneous	12	15.5

This is the indication which is most difficult to assess. Arbuse and Schechtman[1] in an excellent review of the subject state "there is no single nervous or mental disorder that is, in itself, an absolute indication for abortion" and emphasize that each case must be considered individually. They point out that abortion itself may precipitate a new psychosis and therefore by termination of the pregnancy the patient may be thrust out of the frying pan into the fire. Psychoses initiated by pregnancy rarely persist after the puerperium and may even clear up completely before term is reached, and from this fact Arbuse and Schechtman conclude that women who show permanent impairment of mentality following childbirth belong to the class of the potential psychotic for whom pregnancy is merely a subsidiary factor in the pathogenesis of the psychosis and upon the mentality of such women therapeutic abortion cannot be curative and indeed may exert a deleterious effect that is more harmful than the continuation of pregnancy.

There is a growing volume of opinion that only very rarely should psychiatric disease

be an indication for therapeutic abortion, and Russell[10] in a series from Los Angeles reported an incidence of only 4.5 per cent for psychiatric disease, with none performed for this reason during the last 9 years under review. In most other series, however, as the number of therapeutic abortions for other conditions has decreased, that for psychiatric disease has remained constant or has even increased.

So often in psychiatric disease the decision whether or not to terminate pregnancy seems to depend on the view, or even whim, of the psychiatrist concerned, and all manner of socioeconomic factors sometimes seem to play a greater part in the decisions than do the purely medical factors. Only rarely does the psychiatrist make a definitive diagnosis—more often symptoms are described or statements by the patient herself are quoted. Even threats of suicide should not be regarded, per se, as an adequate indication for therapeutic abortion. Greenhill[3] says "according to McLane the suicide rate among women of childbearing age is about the same as that for the total female population but in 1953 in New York the incidence of suicide among pregnant women was only one tenth of this rate."

Surely more careful assessment of the patient's condition by both the psychiatrist and the obstetrician, a greater effort by the psychiatrist toward treatment and wider use of institutional care, and, where indicated, electroshock therapy would reduce the number of therapeutic abortions performed for psychiatric reasons.

Neurological disease

There were 8 therapeutic abortions (10.4 per cent) for neurological disease, 6 being for multiple sclerosis, 1 for epilepsy, and 1 for myasthenia gravis. This incidence would seem to be high as it is generally agreed there is no good evidence that pregnancy has an adverse effect on multiple sclerosis. However, 2 of these patients were almost completely bedridden and in these circumstances therapeutic abortion was justifiable. Epilepsy, per se, is not an indication for therapeutic abortion but where the number of seizures was greatly increased during a previous pregnancy or where status epilepticus has occurred it is usually advisable to terminate the pregnancy.

Hypertensive disease

There were 10 cases (13.0 per cent) in which hypertension at the time of therapeutic abortion or hypertension and/or preeclamptic toxemia in a previous pregnancy was the indication. Three of these patients were obviously very ill (as evidenced by severe hypertension, retinal changes, and elevated blood urea nitrogen levels) when the therapeutic abortion was performed. In the other 7 cases the blood pressure was not unduly elevated and there was no albuminuria at the time of the therapeutic abortion and there would appear to have been no very sound reason for interference. One would venture the opinion that these pregnancies might have been allowed to continue and appropriate measures taken only if and when further complications arose.

Heart disease

There were 8 cases (10.4 per cent) of heart disease—7 of rheumatic heart disease and 1 of congenital heart disease. The latter was a case of auricular septal defect without evidence of decompensation, and socioeconomic factors seemed to have played a large part in the decision to terminate the pregnancy. Advances in cardiac surgery are helping to reduce the incidence of heart disease as an indication for therapeutic abortion since in some cases it is now possible to perform valvulotomy during pregnancy rather than therapeutic abortion. Also, it should always be borne in mind that bed rest followed by vaginal delivery at term may be less of a strain to the patient with heart disease than an abdominal hysterotomy performed in the earlier months.

Renal disease

Renal disease was the indication for therapeutic abortion in 4 cases (5.2 per cent). One was a case of acute nephritis in which

curettage was performed in the sixth week of pregnancy. Two were cases of severe chronic glomerulonephritis, and abdominal hysterotomy and tubal ligation were performed. One of these patients died of the chronic nephritis 4 years later. The fourth patient had had a previous nephrectomy and abruptio placentae in a previous pregnancy. This group would seem to be the one with the soundest indication for therapeutic abortion, and it will be noticed that it comprises only 5.2 per cent of the total.

Previous carcinoma

There were 4 cases (5.2 per cent) in which previous carcinoma was the indication for the therapeutic abortion. Two of these were in the same patient—on the first occasion 2 weeks after a radical mastectomy for breast carcinoma and on the second occasion 2 years later when metastases had developed. Of the other 2, one had had a previous spindle cell carcinoma of the tongue and the other a neurosarcoma of the foot. In these cases humanitarian rather than purely medical reasons were probably taken into account, as no convincing evidence has been produced which shows that subsequent pregnancy affects adversely the prognosis in extrauterine malignancy. While it may be preferable that such patients should not become pregnant it is not necessarily good treatment to terminate pregnancy once it has occurred.

Fetal indications

Possible fetal abnormality would appear to be the indication for therapeutic abortion which is most open to question. In the present series there were 4 cases (5.2 per cent)—1 of rubella and 3 in which 2 or more consecutive pregnancies had resulted in grossly abnormal children. It is now agreed that the chances of an abnormal fetus resulting from an attack of maternal rubella in the early weeks of pregnancy are very much less than found by Gregg[4] and that therapeutic abortion is probably not indicated. The incidence of cases of maternal rubella seems to be falling as women become aware of the problem and are given gamma globulin following exposure in early pregnancy. Where several previous pregnancies have resulted in abnormal children a geneticist may be of help in predicting the possible outcome of a further pregnancy. In these cases it may be difficult to refuse the parent's request to terminate the pregnancy, yet the indication for doing so does not seem to be a very sound one.

Miscellaneous

This miscellaneous group comprised a mixed group of indications too varied to classify and in some of these it is very difficult to understand why therapeutic abortion was agreed to. Table III lists these various indications which comprised 15.5 per cent of the series.

Table III. Miscellaneous indications for therapeutic abortion

Disorganized and infected hip arthroplasty	1
Arthritis of spine and sacroiliac joints	1
Recent spinal fusion	1
Advanced, but inactive, pulmonary tuberculosis	1
Bronchiectasis and asthma	1
Diabetes insipidus with severe asthma	1
Hodgkin's disease	1
Persistent vaginal bleeding, (?)hydatidiform mole	1
Following recent fenestration operation for otosclerosis	1
Hydatid cyst of liver	1
Two previous cesarean sections and failure of tubal ligation	1
Rape in a girl aged 13	1

Method

The various methods by which therapeutic abortion was performed are listed in Table IV.

Table IV. Method of performing therapeutic abortion

Abdominal hysterotomy and tubal ligation	44
Abdominal hysterotomy	2
Curettage	27
Curettage and tubal ligation (1 per vaginam)	2
Curettage followed by subtotal hysterectomy	1
Vaginal hysterectomy	1

In many cases in which it is decided that therapeutic abortion should be performed there is unlikely to be any future improvement in the patient's condition and thus tubal ligation should also be carried out. This fact undoubtedly accounts for the high incidence of abdominal hysterotomy since, of 46 patients who had a tubal ligation, abdominal hysterotomy was performed in 44. In the present series only one patient had an elective hysterectomy. In the patient who is going to have a therapeutic abortion and tubal ligation, total hysterectomy (either abdominal or vaginal) with preservation of ovaries should be considered, especially if she is approaching menopausal age.

Morbidity

There were no deaths in the series and in only 4 cases (5.2 per cent) were there any postoperative complications. In one case the uterus was perforated during curettage and immediate subtotal hysterectomy was proceeded with. One case of abdominal hysterotomy developed a small bowel obstruction due to adhesions to the uterine scar and the abdomen had to be reopened. In 2 other cases of abdominal hysterotomy one patient developed a postoperative pulmonary atelectasis and the other postoperative pyrexia of undetermined cause.

Comment

All of a physician's efforts should be directed toward the saving of human life. Each case of therapeutic abortion means the destruction of a human life and thus no physician should make the decision to interrupt a pregnancy unless he is convinced that the life of the mother is in grave danger if the pregnancy is allowed to continue. There is no operation which is more distasteful to the conscientious gynecologist and it would seem that, at times, it is undertaken without due consideration of the possible alternatives.

In psychiatric cases therapeutic abortion may offer the psychiatrist an apparently easy solution to his and the patient's problems. Not infrequently, however, the patient develops a guilt complex or other psychosis following the therapeutic abortion and this may be more serious than the initial condition.

When confronted with pregnancy superimposed on some disease process the physician with little knowledge or experience of pregnancy may tend to advise therapeutic abortion without realizing fully its possible effects on the patient. Termination of any pregnancy, even in the first 10 weeks, is never an easy procedure and may lead to considerable blood loss, while after 10 weeks an abdominal operation usually is necessary. In some cases this abdominal operation presents more of a risk than does careful supervision of pregnancy and vaginal delivery at term.

The general surgeon often regards pregnancy, when it supervenes on some surgical condition, as a nuisance and will advise its interruption with little consideration of the effect this will have on the patient. The majority of patients who become pregnant greatly desire the pregnancy and are prepared, or even expect to undergo certain discomforts, inconveniences, and risks because of it. To advise its termination without due consideration of these desires and hopes may make the patient's ultimate condition worse than that before she became pregnant.

Sometimes the obstetrician-gynecologist is looked upon merely as the technician who will perform the operation and is expected to have very little opinion in the decision whether or not to interrupt the pregnancy. His experience of pregnancy and labor should be invaluable in helping to arrive at a decision as to how it will affect a particular patient or a particular disease process, and thus in the final decision his opinion should carry considerable weight.

Personalities, too, become involved and pressure may be brought to bear on the physician by the patient or her husband and all manner of social and economic problems may be pressed as a reason for interruption of pregnancy. Referring to eco-

nomic factors, social factors, and convenience Moore and Randall[8] state, "To deny that these forces had not influenced us would be incorrect, to accept them would be unwise, and the best course would be to view future indications in the light of strict medical principles." Guttmacher[5] and other writers have described how a committee of hospital staff members should consider all proposed therapeutic abortions and such a scheme would appear to have a great deal of merit. Such a committee could, and should, be completely objective and impartial and would make the task of refusing requests for therapeutic abortion much easier while at the same time offering more protection to the physician in those cases where it is advised.

As our knowledge increases, therapeutic abortion should become a less common procedure. Today the majority are done for psychiatric reasons and when the incidence for this indication can be reduced, as it has in other conditions, very few therapeutic abortions will be really necessary. All obstetrician-gynecologists will welcome this day.

Summary

Seventy-seven cases of therapeutic abortion performed during the 7 years, 1953 to 1959, at the Winnipeg General Hospital have been reviewed.

The incidence of therapeutic abortion to delivery was 1 to 373.

Psychiatric disease was the most common indication for therapeutic abortion, accounting for 35.1 per cent of the total.

The methods by which therapeutic abortion was performed are listed. Abdominal hysterotomy and tubal ligation was the method in 57 per cent of cases.

It is suggested that by more careful assessment of each case, especially in cases of psychiatric disease, the number of therapeutic abortions could be reduced considerably.

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Vulvar carcinoma

A review of 50 cases—1936 to 1957

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THIS paper presents a review of 50 cases of vulvar carcinoma seen at the Victoria General Hospital in Halifax from July, 1936, to July, 1957. Their incidence is so scattered that very few were seen in any one place in any single year by any one physician. The patients' ages ranged between 28 and 85 years (Table I) and 70 per cent of the total number were over 60 years. The average age was 64.8 years and the median was 66.5.

Delay in diagnosis and treatment

In 46 cases vulvar carcinoma had given symptoms for an appreciable length of time before final diagnosis was made and treatment considered. This was attributable to patient delay in 26 cases, to physician delay in 10 cases, and to both in 10 cases.

Patient delay ranged from 1 to 36 months and averaged 9.6 months. Physician delay ranged from 1 to 17 months and averaged 4.8 months. When both were at fault delay in treatment from 3 to 38 months occurred, averaging 16 (13.1 and 2.9) months. It is noteworthy that one half of the cases of physician delay followed patient delay. It should be remarked that the fact that a vulvar lesion has been present for some time when the physician is first consulted should not foster the impression that it is probably benign.

In this series 18 of the 20 patients whose final diagnosis was delayed were given salves or other useless forms of treatment during the delay period.

Symptomatology

Thirty-two patients complained, when first seen, of a lump in the vulva. Twenty-seven noticed pruritus and irritation about the site of the lesion. Twenty-two complained of bloody discharge. Dysuria was present in 18 and was associated with lesions in the anterior vulvar region in all cases.

The exact frequency of these symptoms as the *main* complaints was not easily determinable, but most patients noticed a vulvar lump first and waited until irritation developed before seeking medical aid. Only 2 patients are recorded as complaining primarily of dysuria.

Other symptoms are listed in Table II.

Physical findings

Types of lesion. An ulcerating, endophytic lesion was found in 16 of these patients, roughly one third of the total group. Fourteen patients bore a single exophytic nodule; 11 presented with a fungating vulvar mass; 4 had fissures only, in each case associated with leukoplakia. Each of these types of lesion was associated with underlying induration in about one third of the cases (Table III).

From Victoria General Hospital.
Presented at the Sixteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Jasper, Alberta, June 10-12, 1960.

Size of lesion. The actual measurements of the lesions were recorded in only 15 cases, but could be estimated from descriptive terms or diagrams in an additional 19. Ten patients (29 per cent) had an initial lesion with a maximum diameter greater than 1½ inches. There was rough correlation between delay in diagnosis and increasing size of the lesion, but this was not well marked and there were anomalies (small lesions present for a long time and large lesions which had grown rapidly) which made statistical evaluation unprofitable.

Site of lesion. The location of the original lesion in various patients is indicated in Table IV. Twenty-three patients had involvement of the labium majus and labium minus on one side. One labium majus was involved in 8 and one labium minus in 3 patients. Both labia, large and small, were affected in 6 cases and in 3 of these the vestibule also was involved. The anterior, middle, and posterior thirds of the vulva were involved in 52, 16, and 32 per cent of the recorded cases, respectively. Other sites of involvement are shown in Table IV. In 3 cases the site was not recorded.

Lymph node involvement. Lymph node involvement was diagnosed on physical examination in 17 cases; none of these were confirmed by histological examination. In one case the lymph nodes of the unsuspected side were found to be affected. Further, in 6 cases lymph node involvement which had been missed clinically was found on histological examination. These findings confirm those of other series and show that attempts to assess metastases clinically are of limited, if any, value.

Associated conditions. Nineteen patients in this series had leukoplakia as well as vulvar carcinoma, and 3 of these also had kraurosis vulvae. Three patients had diabetes with vulvitis. One patient had carcinoma of the cervix.

There were 6 patients in the group who had heart disease of varying severity—hypertension in one and arteriosclerosis in 5. One of the 5 also had bundle branch block.

One patient had hypertension without heart disease. In only one of the 3 diabetic patients was the condition so severe as to require insulin. One patient had pernicious anemia and one had syphilis. (The syphilitic patient was aged 36—one of 3 patients less than 40 years of age, and 27 years younger than the average for the entire group. This would lend a modicum of support to Green's[1] findings that syphilis predisposes to an earlier onset of vulvar carcinoma.)

Pathology

The pathological type of vulvar carcinoma was recorded in 45 of these patients (Table V). Forty-one patients had squamous cell carcinoma and 2 had adenocarcinoma (one of urethral gland and one of sweat gland

Table I. Age distribution

*Age**	*No. patients*	*%*
21-30	1	2
31-40	2	4
41-50	3	6
51-60	8	16
61-70	19	38
71-80	12	24
81-85	4	8
	50	100

*Age range: 28 to 85.

Table II. Symptomatology

Symptom	*No. patients*	*%*
Lump in vulva	32	64
Pruritus and irritation	27	54
Bloody discharge	22	44
Dysuria	18	36
Discharge	13	26
Pain	8	16
Ulcer	8	16
Dyspareunia	2	4
Weight loss	2	4

Table III. Type of lesion*

Ulcerating, endophytic	16
Single nodule, exophytic	14
Fungating mass	11
Fissure	4
Exophytic and endophytic	2
Unrecorded	2

*About one third of each group was associated with diffuse local induration. Six patients had two lesions.

origin). One patient had a melanoma and another had a rodent ulcer.

Distribution of the various grades[2] of squamous cell carcinoma is also shown in Table V. Of all the factors studied it is this pathological classification of the lesion which is most closely correlated with survival. Thus, the survival rates for patients with Broder's Grade I, II, III, and IV, disease were respectively 75 per cent, 58 per cent, 25 per cent, and zero. The patient with the rodent ulcer survived. The patients with the melanoma and the adenocarcinoma did not survive.

Table IV. Site of lesion

Site	*No. patients*	*%*
Labium majus and minus (unilateral)	23	46
Labium majus only	8	16
Labia majura and minora (bilateral)	3	6
Labium majus and minus and vestibule	3	6
Labium minus only	3	6
Clitoris	3	6
Labium majus (bilateral)	1	2
Labium majus, minus, and urethral orifice	1	2
Perineum and labium majus	1	2
Bartholin gland (sweat gland?)	1	2
Not stated	3	6
Total	50	100
Part of vulva involved (recorded in 38 cases)		
Anterior	20	52
Middle	6	16
Posterior	12	32

Table V. Pathological type

Type	*No. patients*	*Survivors*	*%*
Squamous cell carcinoma	41		
Grade I	16	12	75
Grade II	12	7	58
Grade III	4	1	25
Grade IV	4	—	—
Undetermined	5	2	40
Adenocarcinoma: sweat gland (?Bartholin's)	1		
Urethral glands	1		
Rodent ulcer	1	1	100
Melanoma	1		
Not determined	5		

Lymph node metastases

Lymphadenectomy was performed in 35 of these 50 patients and in this group involved nodes were found by histological examination in 13 cases or 37 per cent. Two other patients had inguinal node biopsies which proved positive.

Of the 15 patients with lymphatic metastases, 14 had inguinal nodes involved, and 5 of these had femoral nodes affected. One patient with an ulcerative lesion of the anterior third of the *left* labium minus had metastases limited to the *right* femoral nodes. No metastases to iliac glands were found in the 7 patients who had them removed.

An attempt was made to correlate node involvement with other characteristics of the initial lesion, but was generally unsatisfactory. As expected, patients with longer periods of delay, larger initial lesions, and involvement of the anterior two thirds of the vulva, were more likely to have affected nodes. However, the frequency differences for each characteristic were small, and unexpected associations were found. In all groups the incidence of node involvement ranged, for the most part, between 33 and 38 per cent. This poor correlation was some value in pointing out, once more, that lymph node metastases cannot be predicted, or ruled out, on a basis of primary clinical findings.

Definite association existed, however, between lymph node metastases and mortality. Only 2 of the patients whose cancer had spread to lymph nodes lived more than 5 years (13.5 per cent). In both of these only the superficial nodes had been involved.

Treatment

Of the 50 patients studied, 44 had some sort of surgical treatment. One patient refused operation and 5 were considered to be beyond help when first seen. No patient was refused treatment because of medical contraindications, though 3 of the patients treated were considered to be poor surgical risks and 6 were fair risks only.

Table VI. Treatment, survival, and recurrence

	Treated +5 years ago			*Treated −5 years ago*		
	No. patients	*With recurrence*	*5 year survival*	*No. patients*	*With recurrence*	*Still living*
Radical vulvectomy						
With total lymphadenectomy	1	1		1	1	
With inguinal femoral and unilateral iliacs	2			2	1	1
With inguinal and femoral lymphadenectomy	7	3	2	7		7
With inguinal lymphadenectomy only	9	3	5	4		3
Alone	3	1	2	2		(1)
Inguinal lymphadenectomy only	2	1	(1)			
Simple vulvectomy only				1		1
Local excision	3	2				
No operation	5	1		1		1
Total	32	12	10	18	2	14

Eighteen patients were treated with radiotherapy in various forms, chiefly as postoperative x-radiation.

Radical vulvectomy was performed in 38 cases, alone in 5 and combined with lymphadenectomy of varying extent in 33. Of these latter, 2 had bilateral inguinal, femoral, and iliac gland dissections. Four had bilateral inguinal and femoral node removal with unilateral iliac lymphadenectomy. Fourteen had bilateral inguinal and femoral lymphadenectomy. Thirteen had removal of the inguinal nodes (Pourpart's and saphenous groups) only (Table VI).

Table VII. Surgical complications

	No. cases	*%*
Mortality		
Postoperative psychosis, dehydration parotitis	1	2.3
Congestive cardiac failure, pulmonary edema	1	2.3
Morbidity		
Wound sepsis	15	34
Wound breakdown without infection	12	27
Temperature 100.04° F. for 48 hours more than 24 hours postoperative (cause undetermined)	2	4.6
Pulmonary embolism	1	2.3
Postoperative psychosis	1	2.3
Paresthesia of hip and thigh	5	11.5
Vaginal stenosis	1	2.3

Two patients were treated by inguinal lymphadenectomy only. One died postoperatively of acute pulmonary edema. The other has had radiation therapy to the local lesion on several occasions, but vulvectomy has not been performed.

Three patients underwent local excision of the vulvar tumors. Two of these were first seen outside this hospital. The other patient presented with a far-advanced lesion which was believed to be beyond definitive treatment and underwent palliative excision of the growth and local application of radium.

Surgical complications

Mortality. Two patients of the 44 operated on died postoperatively (Table VII). One of these, in 1940, was an 81-year-old woman who was considered to be a poor operative risk because of arteriosclerotic heart disease. It was felt, however, that she could withstand a staged operation and the first stage—inguinal lymphadenectomy—was performed. The postoperative course was turbulent, marked by congestive failure and gangrenous sloughing of both inguinal regions. She died in pulmonary edema on the sixteenth postoperative day.

The other death occurred in 1942. This patient, a 79-year-old woman, was in relatively good condition preoperatively. She underwent radical vulvectomy without groin dissection. Following the operation she be-

came psychotic, with manic manifestations, followed by withdrawal. For the last 2 weeks she would neither eat nor drink and parenteral hydration was attempted without success. She developed parotitis, with subsequent cervical cellulitis, and died on the forty-third postoperative day.

Morbidity. By far the most frequent postoperative complication was wound breakdown. This occurred in 27 cases of the 38 in which wound healing was recorded. We might perhaps assume that the other 6 patients healed completely and well. In the group recorded, 30 patients had had both vulvectomy and node dissection. Of these, the entire wound area sloughed in 5. In 12 others the vulvar region healed well but both inguinal sites broke down, and in one patient there was a small region of vulvar slough only. Five patients healed completely by first intention.

In both patients who had inguinal dissections only, the entire operative site broke down. The 6 patients who had vulvectomy only healed completely by first intention.

Two efforts at repair by secondary grafting were made, but both failed.

Of the 27 patients who suffered wound breakdown, 15 had associated infections as indicated by prolonged high temperature with local redness, swelling, and purulent discharge. In 12 patients breakdown existed without these manifestations of sepsis.

Final healing occurred in all cases after varying periods of time, some prolonged. Several patients were discharged with unhealed but granulating wounds and instructed in their care to be carried out at home.

Besides the above-mentioned febrile courses, 2 patients had temperatures of over 100.04° F. for 2 days more than 24 hours postoperatively. No cause was found in either case, but neither was serious and both resolved quickly.

Besides the above-mentioned febrile complications 5 patients complained of paresthesia about the hip and thigh of one side. There was one case of phlebitis and one of pulmonary embolism—neither serious. One patient suffered a moderately severe postoperative psychosis.

One patient had troublesome vaginal stenosis which was treated with some success by vaginal dilators.

Time in hospital

Hospitalization time for this entire group ranged between 12 and 115 days, averaging 33.2 days. Patients who had no complications, however, stayed an average of only 25 days (12 to 45 range), whereas the stay for patients who suffered complications ranged from 26 to 115 days and averaged 46.5.

Survival

Thirty-two of the patients reviewed here were treated before 1953 and are susceptible to assessment in terms of 5 year survival. Ten of these patients, or 31.3 per cent, lived 5 years and one died 4 years and 2 months after treatment of extraneous cause (coronary occlusion) (Table VII).

Of these 10 patients, one developed a local recurrence after 4 years, which was treated with radium. This was apparently successful at the time this study began (July, 1957) and she was originally considered to be alive and well 6 years after the original treatment. She has since been found, however, to have renewed local recurrence.

One patient has lived for 6 years without return of local malignancy, but has persistent leukoplakia. Two patients developed recurrence 7 years after the initial treatment and died of the recurrence.

Thus, of the 32 patients treated before 1953 only 7 (22 per cent) can be considered to have been truly cured. If the patient who showed no sign of recurrence at her death of coronary artery disease, 4 years after treatment, may be considered cured the rate rises to 25 per cent.

It is of interest to note that 2 of 10 patients who were well for approximately 5 years after treatment subsequently developed recurrence and died. One patient had had a vulvectomy and inguinal lymphadenectomy, the other had had vulvectomy only, followed by x-ray therapy.

Relationship of survival to treatment

One patient, who had a small focus of very early squamous carcinoma Grade I with kraurosis, was treated by radical vulvectomy only, followed by x-ray therapy, and had been cured (15 years). Otherwise no cure was achieved by any treatment but radical vulvectomy and inguinal node dissection.

Radiotherapy, in conjunction with operation, cannot be evaluated as to its effect on survival because of the great variety of treatment used in a small number of cases.

In considering the effect of operation, we find that the highest percentage of cure for any one treatment group was achieved with those patients who underwent radical vulvectomy and superficial inguinal lymphadenectomy. In this group, 5 of 9 survived.

Of 9 patients treated similarly, but with bilateral femoral node dissection as well, only 2 have been cured. No patient whose treatment included pelvic (iliac) lymphadenectomy—unilateral or bilateral—survived for 5 years.

These anomalies (this since Collins[3] reports better results with more extensive operation) probably spring from two factors. It may be that our most extensive surgical procedure has not been quite extensive enough, or that those who were treated most extensively in this series were those in whom the disease had spread the farthest.

Eighteen patients have been seen since 1953. One has refused treatment. One was treated with simple vulvectomy (1956) and is to date alive without recurrence. Two patients had arteriosclerotic heart disease (at 73 and 81 years of age) and, scheduled for two-stage operations, underwent vulvectomy. One did not have inguinal lymphadenectomy and died of the heart disease 3½ years later without evidence of recurrence. The 81-year-old woman, who also had bundle branch block, refused the second stage of the operation and has since returned with inguinal metastases.

The remaining 14 patients seen since 1953 have been treated by vulvectomy and inguinal lymphadenectomy, the extent of the latter having been determined by the operative findings. One patient had a second stage laparotomy and pelvic gland dissection following pathological diagnosis of femoral gland involvement. She died of metastases, nonetheless, within 2 years. Two patients have had unilateral iliac lymphadenectomies. One developed vulvar and vaginal recurrence and died. The other now has pelvic metastases.

Seven patients have had radical vulvectomy and inguinal and femoral node dissections and 4 have had radical vulvectomy and inguinal lymphadenectomy only. All are to date living and well.

Recurrence

There was a recurrence, after apparently successful treatment, in 14 patients. In 8 cases there was inguinal recurrence, once combined with vulvar return. The vulva and vagina were both involved in 2 cases and were involved individually in 2 cases each. The time of recurrence varied between 4 months and 8 years after the original treatment.

Only one patient has survived recurrence. She underwent excision of a cancerous inguinal gland 9 months after the original treatment and has since survived 20 years without further trouble.

Summary

Carcinoma of the vulva is a disease of old people; it is relatively rare and, as in all carcinomas, survival is closely linked with early diagnosis. This disease process should be treated by a team drawing from a large population area. The treatment of choice is radical one-stage vulvectomy with bilateral inguinal and femoral canal dissection. In this material local recurrence was present in the majority of cases pointing to inadequate surgical attack.

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Fetal loss in cesarean section

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THIS review of cesarean sections performed in the Royal Alexandra Hospital, Edmonton, was undertaken primarily to study the fetal loss in comparison with the total fetal loss.

The hospital is an open general hospital with a separate maternity building. The staff is composed of a number of general practitioners and certified obstetricians and at present 40 to 45 per cent of the patients admitted have received their prenatal care from general practitioners. These patients are attended in the hospital by their own physician unless some complication requires a consultation. All major obstetric procedures and cesarean sections are performed by certified obstetricians.

The hospital perinatal committee follows the standard of viability and the coding procedure of the Provincial Perinatal Committee which, until 1960, used 1,000 grams and 28 weeks' gestation as the standard of viability. These limits have now been lowered to 750 grams and 24 weeks' gestation.

All infants delivered by cesarean section are admitted directly to the observation nursery which is operated in conjunction with the premature nursery for the hospital, before being transferred to the regular floor nursery.

During the 5 year period reviewed, there were 20,065 deliveries and 312 twins. A total of 577 cesarean sections were performed including 11 which resulted in the birth of twins. In this period the cesarean section rate has not varied greatly except for 1958, but a review of the indications for operation in that year fails to reveal any gross deviation from the usual pattern.

The average section rate was 2.21 per cent (Table I). To a minor degree, this rate does not reflect the actual practice in the hospital because a certain number of patients are admitted for their final cesarean section who have been delivered previously in hospitals where sterilization is not performed.

From the Royal Alexandra Maternity Hospital and the University of Alberta Medical School.

Presented at the Sixteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Jasper, Alberta, June 10-12, 1960.

Maternal mortality

Two mothers died following cesarean section. The first was a 39-year-old gravida iii who had weighed over 200 pounds since age 20 and was suffering from hypertension with superimposed pre-eclampsia. Her youngest child was 10 years old. Cesarean section was performed after ineffective medical induction. Death resulted from pulmonary embolism on the third postoperative day.

The second patient died from acute bulbar poliomyelitis 10 days after admission. She was in the thirty-seventh week of gestation and was delivered of a living baby by cesarean section two days after admission.

Obstetric trauma

During this 5 year period there were 2 instances of rupture of the lower uterine segment, one from extension of an old cervical laceration, and one a transverse laceration in the lower uterine segment. The

Table I. Cesarean section rate and perinatal death rate

Year	Deliveries	Cesarean sections	Rate (%)	Fetal loss per 1,000 births			
				Hospital total	Cesarean section		
					No.		
					Newborn	Stillborn	Rate
1955	4792(+60)*	102(+2)*	2.13	23.5	5	0	48.0
1956	5048(+64)	106(+1)	2.10	24.6	3	1	37.4
1957	5180(+47)	107(+3)	2.17	24.8	5	2	63.6†
1958	5435(+79)	146(+4)	2.68	20.7	6	1‡	40.0
1959	5610(+62)	116(+1)	2.08	30.0	3	0	25.8
Total	26065(+312)	577(+11)	2.21	22.7	22	4	44.2

*Twins.
†Four of 5 neonatal deaths associated with placenta previa.
‡Birth weight 565 grams.

first resulted from an assisted breech delivery in a para ii with a 9 pound infant. The patient survived after abdominal hysterectomy. The other occurred in a para i with a 7 pound infant delivered by version and extraction for prolapsed cord. This patient survived after repair of the laceration.

One maternal death followed a chain of events that possibly had its beginning in a vault laceration incurred in the delivery of a 10 pound, 14 ounce stillborn infant. This patient received unmatched blood and developed anuria, but died of septic pulmonary emboli and acute bronchopneumonia.

Perinatal deaths

Table I reveals a perinatal loss for all deliveries of 22.7 per 1,000 births while the loss associated with cesarean section was 44.2. It will be noted, however, that in 1959 the total perinatal loss has been reduced to 20 per 1,000 births and that the loss associated with cesarean section approached the same rate, having diminished to 25.8.

The fetal loss associated with cesarean section is comprised of 22 newborn and 4 stillborn infants. An autopsy was performed on 20.

In 1957, 4 of the 5 neonatal deaths were associated with placenta previa, and the stillborn infant in 1958 weighed only 565 grams.

Table II. Type of operation and anesthesia

Year	No.	Type of operation			Type of anesthesia	
		Low transverse	Cesarean hysterectomy	Classical	Spinal	General
1955	102	88	3	11	95	7
1956	106	100	0	6	101	5
1957	107	103	0	4	97	10
1958	146	129	5	12	116	30
1959	116	106	0	10	84	32
Total	577	526	8	43	493	84

Type of operation

It is apparent from Table II that few cesarean hysterectomies are performed, this procedure being restricted largely to cases of myomata uteri. It is probable, however, in view of the experience of others who have used this operation more frequently and with safety, and in the best interest of certain patients, that the uterus should be removed more often at the time of the final section.

The so-called "classical" entry to the uterine cavity is rarely employed—being utilized only in certain cases of placenta previa and at times when the lower uterine segment is difficult to expose.

At repeat section, following a previous low transverse incision in the uterus, defects of varying size and degree are not uncommon. These, however, have never resulted in any serious complications and there appears to be no reason to perform a repeat

section before term for fear of scar disruption. Therefore, it is felt that allowing all patients for repeat section to continue to term or until labor begins, rather than terminating the pregnancy at a calculated date short of term, will avoid the risk of delivery of an occasional premature infant.

Anesthesia

It is interesting to note, too, that in the last 2 years there has been an increase in the use of general anesthesia. There are two factors that have influenced this trend: first, the advances in anesthetic agents and techniques of administration have made general anesthesia more suitable for this operation; second, the fear that, should complications follow spinal anesthesia, such a procedure might be difficult to justify in court since some neurologists are quite positive in their view that spinal anesthesia is dangerous and should not be used.

Fetal loss

In studying the clinical and pathological features of the babies that died, one finds the most common picture to be one of clinical respiratory failure, and after autopsy the pathologist usually reports "hyaline membrane disease" and "atelectasis." It is proposed, therefore, for the sake of brevity and simplicity, to designate this clinical and pathological picture as "respiratory distress syndrome" (RDS).

Table III. Fetal loss and maternal state

Primary section		
Placenta previa		8
Abruptio placentae		3
Diabetes mellitus		2
Abnormal presentation		2
Eclampsia		1
Acute poliomyelitis		1
Incoordinate uterine action and pre-eclampsia		1
Repeat section		
Premature labor; 35 weeks; 3 pounds, 12 ounces; respiratory distress syndrome		1
Premature labor; 35 weeks; 3 pounds, 9 ounces; respiratory distress syndrome		1
Acute hydramnios; 33 weeks; 3 pounds, 4 ounces; stillbirth (previous classical)		1
Elective		5
Cardiac hypertrophy	1	
Diaphragmatic hernia	1	
Respiratory distress syndrome	1	
Erythroblastosis	1	
Breech, spina bifida	1	

Eighteen babies were lost at the first section, the majority of these having been delivered of patients suffering from antepartum bleeding—8 with placenta previa and 3 with premature separation (Table III).

The 2 diabetic mothers were delivered electively at 35 weeks. The babies weighed 8 pounds, 2 ounces and 6 pounds, 14 ounces, respectively, and both died of RDS. One lived only 9 hours while the other lived 43 hours. One pregnancy was terminated at 26 weeks because of acute fulminating eclampsia in an unmarried mother who had had no prenatal care. The infant weighed only 565 grams.

One patient with pre-eclampsia had labor induced with some difficulty. Cesarean section was performed after 60 hours of poor labor and 24 hours after artificial rupture of the membranes. The baby died of pneumonia. This case was coded preventable and "physician error in judgment."

One cesarean section was performed on a patient with acute bulbar poliomyelitis.

It will be noted that of the 8 babies lost at repeat section, 3 were premature—2 due to premature labor—and both died of RDS. The third was stillborn at 33 weeks; the mother had had a previous classical section and developed acute hydramnios. This infant was microcephalic.

Of the other 5 babies delivered by elective repeat section, one had the typical picture of RDS and one had moderate cardiac hypertrophy, atelectasis, and chronic passive congestion. The other three had conditions incompatible with life.

Antepartum bleeding

Table IV reveals our experience with antepartum bleeding. Eighty cesarean sections were performed for this complication —13.86 per cent of the total—with a total fetal loss of 11, or 13.75 per cent.

In 1959, however, only one baby was lost and its death could not be attributed either to the antepartum bleeding or to the operation. This infant died on the ninth day of life. Its progress had been satisfactory until it accidentally became overheated from being too close to a radiator. The autopsy diagnosis was "acute hemorrhagic pneumonia."

Two of the 11 were stillborn (one anencephalic). The remaining 8 died of RDS—all proved by autopsy.

The records of the mothers of these 8 reveal severe blood loss and some degree of shock before resuscitation and operation. This would suggest that prompt delivery of the infant, to prevent excessive blood loss, is imperative; and, to prevent such circumstances, the bleeding patient should be watched carefully.

Neonatal deaths

The RDS was diagnosed in 16 of the 22 cases of neonatal death—in 14 at autopsy (Table V). The 2 cases of pneumonia must be considered as preventable—the first resulting from a "physician error in judgment" and the second from an unfortunate incident in the premature nursery. The remaining 4 had congenital abnormalities incompatible with life and beyond correction or treatment.

From Table VI it is apparent that one half of the total deaths from RDS occurred in association with antepartum bleeding and that RDS was the cause of death in 10 per cent of the babies delivered by cesarean section of mothers with antepartum bleeding, but in only 1.2 per cent of babies whose mothers underwent cesarean section for all other indications. The average weight of the 8 infants associated with antepartum bleeding was 4 pounds, 7 ounces, and the average period of gestation was 34 weeks. It would thus appear that the weight and age of these infants may not be the determining factors in their failure to survive, for it is reasonable to expect fewer fatalities in infants of this weight and age. However, as previously noted, the mothers of these 8 infants suffered severe blood loss before operation.

Table IV. Fetal loss in antepartum bleeding

Year	*Total sections*	*Sections for antepartum bleeding*	*Fetal loss*
1955	102	12	1 (8.5%)
1956	106	12	1 (8.5%)
1957	107	15	5 (33.0%)
1958	146	20	3 (15.0%)
1959	117	21	1 (5.0%) (death 9th day)
Total	577	80 (13.86%)	11 (13.75%)

Table V. Neonatal deaths

Respiratory distress syndrome	14	(Autopsy)
	2	(Clinical)
Pneumonia	2	After 60 hrs. labor, lived 3 days
		Acute, 9 days of age
Congenital defects	3	Diaphragmatic hernia, lived ½ hour
		Brow presentation, meningocele
		Breech plus spina bifida (2 previous sections)
Erythroblastosis	1	Lived 3 hours
Total	22	

Table VI. Neonatal deaths from respiratory distress syndrome

Maternal state	*No.*	
Antepartum bleeding	8	(10% of 80 sections)
Repeat section	4	1.2% of 497 sections
Diabetes mellitus	2	
Acute poliomyelitis	1	
Eclampsia (26 weeks)	1*	
Total	16	

*Weight, 565 grams.

Table VII. Stillbirths

Previous classical—acute hydramnios—33 weeks—weight 3 pounds, 4 ounces—microcephaly
Placenta previa—35 weeks—weight 3 pounds, 10 ounces—marked blood loss
Abruptio placentae—age 44—hypertension—transverse lie—anencephaly—severe bleeding
Transverse lie—41 weeks

Our experience with antepartum bleeding, therefore, would suggest some relationship between the maternal state and the occurrence of the respiratory distress syndrome.

Stillbirths

The 4 stillbirths are listed in Table VII. Possibly the first of these mothers could have been delivered vaginally had the fetal diagnosis been made preoperatively; since the previous classical scar did not rupture with the development of hydramnios, it would probably have withstood the delivery of a small fetus. The other 3 stillbirths were unavoidable.

Summary

1. The cesarean section rate for the years 1955 to 1959 was 2.21 per cent.

2. There was one maternal death from pulmonary embolism and one from acute bulbar poliomyelitis.

3. The average perinatal loss for all deliveries in the hospital was 22.7 per 1,000 births, and for cesarean section the average loss was 44.2 per 1,000 births. In 1959 these rates were 20.0 per 1,000 births for all deliveries and 25.8 per 1,000 births for delivery by cesarean section.

4. The total fetal loss with cesarean section was 26, comprised of 22 neonatal deaths and 4 stillbirths. One infant weighed only 565 grams and 6 others had congenital abnormalities incompatible with life.

5. Sixteen of 22 neonatal deaths were due to the respiratory distress syndrome and one half of these were associated with antepartum bleeding. This cause of fetal loss occurred in 10 per cent of cases when operation was performed for antepartum bleeding but in only 1.2 per cent when operation was performed for all other indications.

6. Antepartum bleeding was the indication for operation in 11 of the 26 perinatal deaths.

Risks in breech delivery associated with fetal size and the induction of labor

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THE risks inherent in breech delivery are well known and are hardly lessened by the mere parity of the patient to be delivered.

Dr. Baetz'[2, 3] most recent summary of the causes of fetal deaths as related to the type of delivery in 7 cooperating Buffalo hospitals records the fetal mortality observed in approximately 250,000 deliveries. When all the correctable causes of fetal loss have been deducted, namely, (1) the nonviable premature infants (until 1955 under 1,500 grams, since 1955 under 1,000 grams); (2) the antepartum deaths (macerated infants); and (3) the infants born with congenital abnormalities incompatible with life, the 4 per cent breech deliveries continue to be associated with more than 25 per cent of our total fetal loss. Actually, breech delivery was associated with 24.6 per cent of the corrected fetal loss in 1957, 24.1 per cent in 1958, and nearly 30 per cent in 1959.

Conversion of the persistent breech to a vertex presentation by external version before the onset of labor has long been advocated. While this procedure continues to be employed routinely in some areas, external version is never attempted by many obstetricians of considerable experience. In this regard, Vartan[7] has long emphasized a rather practical concept. At 32 to 34 weeks' gestation, if examinations have been made frequently, he believes that the fetus can be found to be presenting by the breech in at least 20 per cent of cases. Vartan believes that breech presentations spontaneously convert to vertex by the onset of labor in all but about 3 per cent of the pregnancies which go to term.

Those who have practiced routine attempts at external version seem agreed that in 10 to 15 per cent of cases they are unable to convert the breech to a vertex by external version. We are tempted to conclude, therefore, that about the same proportion of breech presentations which can be converted to vertex by the techniques of external version can also be expected to convert spontaneously to a vertex before the onset of labor *if* pregnancy goes to term. The ones that persist as breech presentations may be the ones in which version would not have been successful anyway. With Vartan's concept in mind, we have admittedly neglected to develop the art of external version.

Consideration of the risks of breech delivery have long emphasized the advantages and disadvantages of the routine practice of assisting the frank breech as soon as full dilatation has been accomplished as compared with the practice of permitting the delivery

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to proceed spontaneously until the umbilicus appears at the introitus. The influence of varying types of anesthesia and the importance of the judgment and skill of an experienced obstetrician have often been emphasized. The risk of breech delivery is apparently less in the hands of the experienced specialist, but is likely to be manifest in the teaching services when delivery is managed by students, interns, and residents.

In the Buffalo area, Potter's[5, 6] definition of the factors accounting for difficulties during breech delivery has contributed greatly to an increased interest in and respect for the risks inherent in breech delivery at term. Perhaps the majority of obstetricians, however, are not yet willing to regard breech presentation alone as adequate indication for elective cesarean section in the nullipara. Many insist that the ability to manage a breech presentation successfully should be regarded as one of the fundamentals to be acquired by the obstetrical specialist.

For years we assumed that we could gather data justifying the acceptance of some fetal loss associated with breech delivery at term in a primigravida for the sake of preserving an unscarred myometrium. It was our conviction that a woman whose first pregnancy resulted in breech delivery was no more likely than the average multipara to have a breech presentation at term in subsequent pregnancies. Actual findings were quite contrary to our expectations. Although Baetz[1] noted that the incidence of breech delivery among primigravidas was approximately 4 per cent, he found that the incidence of a second breech presentation was approximately 21 per cent. It seemed evident, therefore, that the factors accounting for breech presentation, at least among those women who had a breech delivery at term as primigravidas, are factors that can be expected to persist and predispose to a breech presentation at term in subsequent pregnancies.

In recent years, the practice of routine exploration of the uterine cavity immediately after the expulsion of the placenta has suggested the probability that irregularities in the contour of the uterine cavity, particularly the presence of incomplete "doubling" or septae in the fundus, are associated with breech presentation in a significant proportion of cases. Consideration of the problems inherent in the management of breech presentation might well continue, therefore, to take into account the probability that the woman whose first baby presents as a breech at term will be likely in subsequent pregnancies to again have a breech presentation at term.

Contrary to what is perhaps a rather general impression, our records also indicate that the fetal loss associated with breech delivery at term in the multipara is not significantly less than that associated with breech presentation at term in the woman's first pregnancy. If elective cesarean section is the safest way to deliver the primigravida with a breech presentation at term, it must also be the safest way to deliver the multipara with a breech presentation at term.

A visiting Professor at the University of Buffalo, Dr. Arthur Sutherland of Glasgow, recently expressed the conviction that the difficulties in breech delivery could be minimized by elective induction of labor as soon as the fetus was thought to weigh 5½ to 6 pounds. Our interest in his suggestion was increased by the fact that elective induction of labor had in recent years become a frequently employed procedure by a number of the obstetricians in the Buffalo area. As a result of this experience, it seemed evident to us that the risks inherent in the elective induction of labor could be reduced if care is taken to make certain that the labor is not initiated while the child is still premature.

Rupture of the membranes when there is maternal or fetal indication to terminate the pregnancy is recognized as the most certain and dependable method of initiating labor.[4] As a means of initiating purely elective induction, however, we continue to feel that such initial rupture of the membranes is not wise. With the breech presenting, rupture of the membranes before the onset of labor, whether this occurs spontaneously or is done electively, increases the risk of a

prolapsed cord. With the vertex "a little high," rupture of the membranes, particularly when the fetus is "a little small," increases the risk of a compound or unfavorable presentation. With vertex or breech presenting, initial rupture of the membranes is not infrequently associated with the maternal risks inherent in an undesirably long latent period. We think, therefore, that each elective induction should be approached with the feeling that the attempt to initiate labor will, to a considerable extent, be only a therapeutic test to see if the pregnancy is really at term and the uterus easily stimulated to contract.

When an infusion of an oxytocic initiates contractions which bring about effacement and dilatation of the cervix, we have reason to feel that, from the standpoint of function, the placenta has served its purpose and the baby is as large as it is going to be. Assuming that placental function is more likely to be keeping the uterus refractory to oxytocics before term than later when both fetus and placenta are "ripe" for induction, we have been proceeding on the theory that we will not be as likely to initiate labor when the infant is still premature if we first see what the effect of an infusion of dilute Pitocin will be before we consider rupture of the membranes. If the uterus fails to respond, we might well conclude that the uterus is not ready for induction. If we then change our mind, convince the patient that labor should not be induced immediately, and send her home, no harm has been done. If the membranes have been ruptured, however, our steps cannot be retraced.

Whether we recognize postmaturity as an entity or not, at times pregnancy seems to have continued until the placenta proves unable to supply the fetus with sufficient oxygen for it to survive the effects of the frequent long contractions characteristic of the "overdue" labor. In such cases, we could have been serving the babies' best interests if we had electively initiated labor at an earlier date. Induction could in this manner be indicated, in a prophylactic sense, but we believe such benefit is likely to be accomplished only if we restrict our efforts to induce labor to those instances in which we find that it can be done easily.

Consider then the proposal to induce labor when breech presentation persists, as a means of assuring delivery of the baby before it becomes as large as it may if the spontaneous onset of labor is awaited. Our interest in this suggestion was increased by previous conviction that the risks inherent in any elective induction of labor would be more likely to be realized if labor is initiated when a small fetus is in the breech position, particularly if the induction is started by elective rupture of the membranes.

Shortly before Dr. Sutherland's visit, a review[4] of the elective induction of labor in two Buffalo hospitals had indicated breech presentation was a contraindication to such elective induction. Dr. Sutherland's proposal was not simply to elect induction in spite of breech presentation, but, rather, that induction of labor, when breech presentation persists, should be undertaken as a considered effort to reduce the fetal loss or injury incident to breech delivery. Before we could agree, we decided to look for evidence that the smaller babies presenting by the breech are more easily and more safely managed during labor and delivery.

The recommendation of induction before term was a disturbing idea because for years we had taught that a relatively big baby in breech presentation, particularly frank breech, could be expected to dilate the cervix and birth canal adequately and thus facilitate delivery of the aftercoming head. When the baby seemed large, we had assumed that delivery of the aftercoming head would be relatively easy. With these possibilities in mind, we were prompted to review again the risks associated with breech delivery which seem particularly related to fetal size. Case records were surveyed in order to compare the results of breech delivery when the babies weighed between 5 and 6 pounds with the results when the babies weighed more than 7 pounds.

In these data, we have disregarded the frequency of fetal injury and morbidity, frac-

tures of fetal extremities, injuries of the brachial plexus, and later evidence of cerebrospastic disease or mental retardation. This omission is due to our own conviction that such injury to the fetus usually occurs when the delivery is managed by a relatively inexperienced operator. In gathering these data, we have attempted to compare results that could hardly be altered by the experience and technical skill of the obstetrician.

In the Buffalo General Hospital during the 10 years 1949 to 1958 there were a total of 20,162 deliveries including 479 breech presentations in which the baby weighed over 5 pounds at birth. This number of breech deliveries at or near term represented 2.4 per cent of the deliveries in this hospital during the 10 year period surveyed. In 90, or 18.8 per cent, of the 479 breech deliveries reviewed, the baby weighed between 5 and 6 pounds. In approximately one half of all breech presentations (234 of the 479 babies), the newborn infant weighed over 7 pounds.

The frank breech was the most frequent type, and, somewhat to our surprise, the size of the fetus was found to have no appreciable effect on the relative frequency of a frank breech presentation. In 259 of the 479 cases (54.1 per cent of the breech deliveries), the fetus presented as a frank breech. Of 90 cases in which the baby weighed 5 to 6 pounds at birth, 50, or 55 per cent, involved a frank breech presentation. Of the 234 cases in which the baby weighed over 7 pounds at birth, 127, or 54.3 per cent, involved a frank breech presentation.

Footling or compound presentation was also not more frequent among either the larger or the smaller babies. There seemed to be no concentration of factors increasing the risk to the fetus in either the smaller (5 to 6 pounds) or the larger (over 7 pounds) group, other than those factors which would be expected to be related to the birth of relatively large or relatively small babies. For this reason, we thought it reasonable not to attempt to "correct" our figures for such factors as premature rupture of the membranes, precipitate labor, or multiparity.

The outcome was to some extent influenced by those secondary factors associated with fetal size. It is evident, for instance, that, when breech presentation persists, spontaneous premature rupture of the membranes is more likely. With the breech presenting, a relatively longer latent period between such premature spontaneous rupture of the membranes and the onset of labor can be expected, and this latent period is likely to be longer when the babies are smaller. In 64 cases in which the baby weighed between 5 and 6 pounds, it was found that the time between premature rupture of the membranes and the onset of labor averaged 15.1 hours compared to an average of only 9.9 hours in 195 cases of breech delivery following premature rupture of the membranes when the babies all weighed over 7 pounds.

A relatively longer period of total time in the labor room, in the presence of a small baby, might be at least partially due to the relative unripeness of the cervix and unresponsiveness of the myometrium. Among our own cases, however, we did not find the correlation we had expected between the length of labor and the size of the baby.

In the primigravidas, when the baby presenting by the breech weighed between 5 and 6 pounds, labor averaged 11.4 hours compared to 18.3 hours when the baby weighed more than 7 pounds. When the mother was a multipara and the baby weighed between 5 and 6 pounds, breech labors averaged 8.8 hours compared to 9.9 hours when the baby weighed more than 7 pounds. The second stage of labor in the primigravida averaged 57.3 minutes when the baby weighed between 5 and 6 pounds and averaged nearly twice that, or 191.5 minutes, when the baby weighed more than 7 pounds. When a multipara had a breech presentation, the second stage of labor averaged 32 minutes when the baby weighed 5 to 6 pounds and 38.6 minutes when the baby weighed over 7 pounds.

Cesarean section was elected before the onset of labor in 1.2 per cent of the cases when the baby weighed between 5 and 6 pounds and in 4.8 per cent of the cases when

the baby weighed over 7 pounds. Among the mothers of smaller babies, 2.5 per cent were delivered by cesarean section after there seemed to be no progress in labor, but when the babies weighed more than 7 pounds at birth 3.5 per cent of the mothers were delivered by cesarean section because labor did not progress.

There was no evidence of a greater risk of prolapse of the cord with the smaller (5 to 6 pounds) babies than with the larger (over 7 pounds) babies. In 5 of the 12 cases in which prolapse of the cord became evident (or 40 per cent), this complication was first recognized during the second stage of labor.

Breech delivery was completed "without difficulty" in 85 per cent of the cases when the baby weighed between 5 and 6 pounds, and with no difficulty in only 70 per cent of the cases when the baby weighed over 7 pounds. Greater difficulty with larger babies is evidenced also in the fact that Piper forceps were used in 12 per cent of the deliveries of the smaller babies and in 21 per cent of the cases when the baby weighed over 7 pounds at birth. It must be admitted, however, that the Piper forceps were at times regarded as a means of affording protection to the aftercoming head of an obviously small fetus, whereas the forceps were not likely to have been elected in the birth of the relatively larger babies for any such purely prophylactic consideration.

Niswander and Patterson[4] have recently reviewed the records of 1,000 consecutive labors which were electively induced during the past 3 years in the Children's and Buffalo General Hospitals. Among the labors reviewed were 22 cases in which the persistence of a breech presentation had apparently not been recognized when the decision was made to induce labor. The outcome in these 22 cases in which labor was electively induced with the breech presenting has been the subject of much local interest.

There were 2 babies in the 5 to 6 pound group. One had no difficulty. In the other the cord prolapsed and, although a cesarean section was performed promptly, the baby did not survive. There were 8 babies in the 6 to 7 pound group. Seven had no difficulty, but one presented as a footling, the cervix dilated rapidly, delivery of the aftercoming head was considered difficult, and the child did not survive. There were 12 babies in the group weighing more than 7 pounds at birth; there was no difficulty with the delivery of any of the 12, and all survived without complication.

Among the cases of breech delivery managed at the Buffalo General Hospital between 1949 and 1958, smaller babies seem more frequently associated with fetal loss. Among the 90 cases of breech delivery when the babies weighed 5 to 6 pounds, the gross loss was 6.66 per cent, correctable to a fetal mortality of 3.33 per cent. This loss among the smaller babies with breech presentation, seems high considering the fact that the corrected fetal mortality, when only babies weighing over 7 pounds were considered, was 1.7 per cent in a total of 234 breech deliveries at term.

It is evident that we may be maintaining a conviction upon the basis of two sets of rather meager data. When labor was electively induced in 22 cases of breech presentation, one of the 2 babies weighing between 5 and 6 pounds and one of the 8 babies weighing between 6 and 7 pounds died, while all of the 12 weighing more than 7 pounds survived without difficulty. In only 2 of those 22 babies with breech presentation was labor induced when the baby weighed under 6 pounds, but in one of the 2 the cord prolapsed and the fetus did not survive. Although this is only a single case, it nevertheless seems a good example of the fact that when the breech is presenting and labor begins when the baby is still small and before it is well down into the pelvis, accidents seem more likely to happen.

Comment

Cases studied are but few, even with a review of breech deliveries in the Buffalo General Hospital during the past 10 years. Can we draw conclusions based on the fate of only 7 babies among the 324 breech de-

liveries considered? What would have happened to our conviction if we had lost 2 instead of 3 among the 90 babies weighing between 5 and 6 pounds, and lost 5 instead of 4 among those weighing more than 7 pounds? Such a shift involving realignment of but one of the 7 fetal deaths would, of course, have reduced the deaths among the smaller babies by 33 per cent and increased the deaths among the larger babies by 25 per cent.

The loss of 2 among 90 smaller babies would have meant a fetal mortality of 2.2 per cent for the 5 to 6 pound group, and the loss of 5 babies instead of 4 among the group weighing more than 7 pounds would have meant a fetal mortality of 2.1 per cent for the larger babies. This would seem to suggest that there will have to be more than a 14 per cent shift in the fetal loss from the smaller to the larger baby groups before we could provide data that would make efforts to assure delivery of relatively smaller babies seem advisable.

Summary

From our data, a comparison of the difficulties experienced with breech deliveries when the babies are small (5 to 6 pounds) and those when the babies weigh more than 7 pounds, three conclusions may be reached:

1. With the smaller babies, there was no increased incidence of prolapse of the cord and no increased incidence of unfavorable footling presentations.

2. With the smaller babies, labor was less frequently difficult and less likely to terminate in cesarean section after a few hours of ineffectual contractions.

3. We can find no reason to believe, however, that we could reduce the frequency of the *fatal* complications of breech delivery by inducing labor when we think the baby will weigh between 5 and 6 pounds.

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Relationship of age to survival rate in carcinoma of the cervix

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THE statement is frequently made that the prognosis of cervical carcinoma in young individuals is poorer than in women of the older age groups. We undertook this study because we were uncertain as to the validity of this claim and because if it could be supported by our own findings it might have some influence in the management of these patients.

A review of the literature reveals two large series in which the statistics were analyzed and the subject carefully considered. Truelsen[8] in his very comprehensive study of carcinoma of the cervix in 1949 found widely divergent statements on the question. He relates that authors such as Heyman felt that it has not been proved that young women have a poorer prognosis than their older counterparts; Voltz, on the other hand, felt that younger women had poorer cure rates in all stages than the entire group, while Dietel and Döderlein found the results to be actually better in the younger age group. Truelsen analyzed 2,450 cases treated between the years 1922 and 1937 and found that the number of patients surviving 5 years was practically constant in all age groups up to 65. When he further divided the various age groups into stages, he found the difference in the survival rate to be only slight and not always in the same direction.

The second large series was reported by Lindell[5] in 1952 and consisted of 5,258 patients treated by radiotherapy in the Radiumhemmet between 1910 and 1944. He noted that 4.03 per cent or 207 patients were under 31 years of age, and he analyzed these further. Truelsen had found 68 patients, or 2.8 per cent, under 30 years of age and did not feel that the number was of sufficient magnitude to be statistically significant. Lindell's tables showed that the 5 year survival rate was 10 to 12 per cent lower in Stages I and II for patients under 31 years of age than it was for the patients of the same stages in the succeeding three decades where they were approximately the same. In Stage III the 5 year survival rate was 8.2 per cent in 49 patients under 31 and was 12.8, 19.5, and 24.2 per cent in the succeeding three decades, respectively. Lindell also noted that the cancer death rate was greatest in the first 2 years after treatment in young women while in women of 50 years and over it was evenly distributed over the 5 years.

Decker, Fricke, and Pratt[3] of Rochester, reporting on the cases seen in the Mayo Clinic from 1940 to 1949, found 149 of 1,451 patients to be under the age of 35. Following an analysis of these cases they concluded that there was no essential difference in the end results of treatment between women under the age of 35 and those over the age of 35. A substantial number of the

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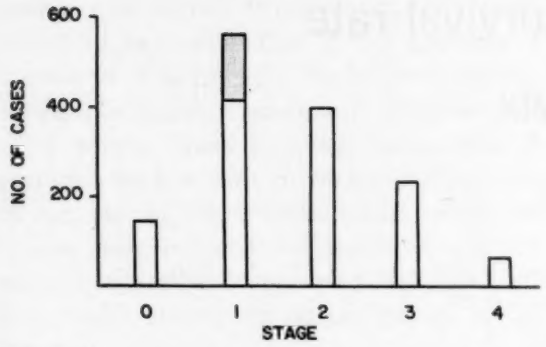

Fig. 1. Incidence of carcinoma of cervix, Royal Victoria Montreal Maternity Hospital, by stage. Stippled portion represents preclinical cases.

patients in Stage I were treated surgically and it was not recorded whether or not there were any preclinical lesions included.

Strobel[7] in 1956 reported on 127 patients under the age of 30, which was 2.54 per cent of the series. The 5 year survival rate in Stage I was 54.5 per cent, in Stage II 27 per cent, and in Stage III 7.2 per cent.

Böttger and Berić[2] in 1958, reporting a series of 1,808 cases, found that 4.1 per cent or 75 patients were under the age of 30 years. Ten of the cases were concomitant with a pregnancy. Nineteen patients or 25 per cent survived 5 years.

Material and methods

The present study is based on the case records of 1,418 consecutive cases of primary carcinoma of the cervix seen in the Royal Victoria Hospital between 1926 and 1959, inclusive. The International Classification was used in staging. It was noted that since 1949 the widespread use of cytological screening has markedly increased the number in Stage 0 and has altered the composition of Stage I by the inclusion of invasive but clinically unappreciable tumors. This preclinical segment of Stage I will be identified in the statistical presentation. In age-stage studies 5 year increments were used. In the age-stage survival studies 10 year increments were used as the series did not appear large enough to permit significant conclusions with the smaller figure. As a basis of "cure" it was decided to use "5 year survivors." This method of analysis renders unnecessary the often very difficult task of ascertaining that a patient alive at 5 years is or is not free of tumor. Patients living less than 5 years but dying of other causes even though considered free of tumor are not considered as 5 year survivors. All patients lost to follow-up are considered

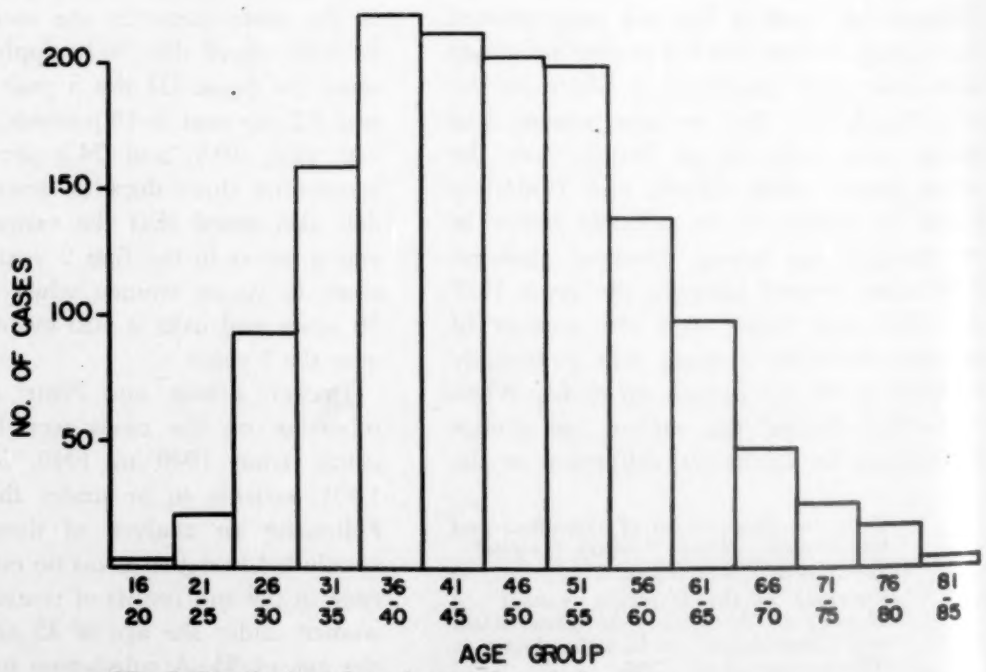

Fig. 2. Distribution of carcinoma of cervix by age.

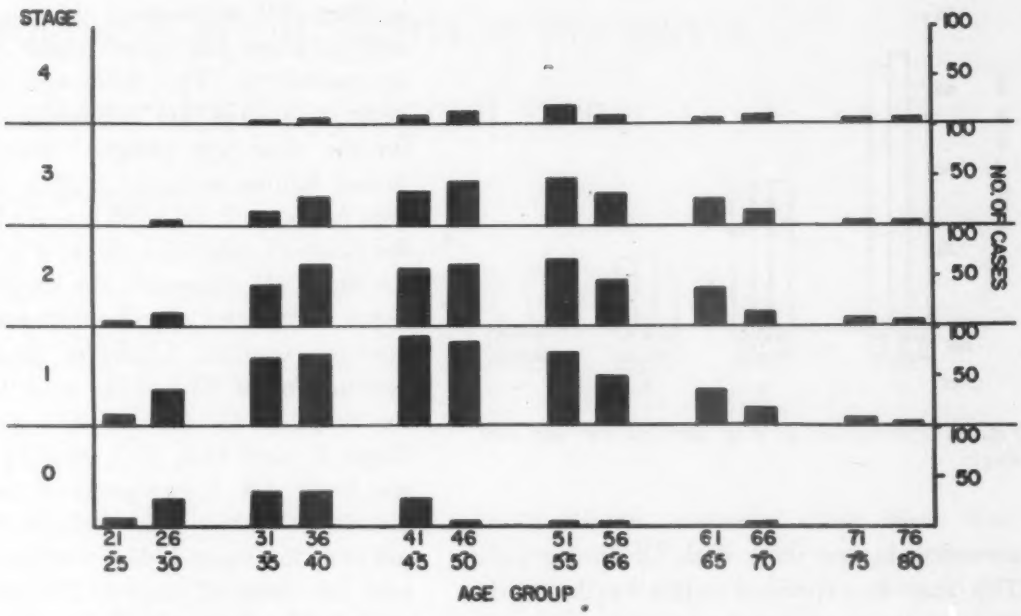

Fig. 3. Incidence of carcinoma of cervix, broken down by age and stage.

dead of tumor. There were only 8 such cases.

Results

Fig. 1 shows the entire series broken down into the 5 International Classification stages with the stippled portion of Stage I representing the preclinical cases.

The clinical staging of any series of cervical cancer is subject to two important limitations. The first is the human variation in the evaluation of the examination. The second is the varying degree of the use of screening techniques by any one clinic.

A wide variation in staging by various authors is noted in the last volume of the *Annual Report on the Results of Treatment of Carcinoma of the Uterus.*[1] Compared to this series there seems to be a tendency to increase the number of cases in Stage II at the expense of Stage I. Fig. 2 is a breakdown of the series into 5 year age groups which in essence is a population distribution curve.

Looking at the two extremes in age grouping one notes that there are only 24 patients of 25 years and under, and 45 patients of 70 years and over. The greatest number of cases is concentrated about equally in the four divisions of the twenty-year period from age 36 to age 55. There are 102 patients under the age of 31. Sixty-eight of these patients have preclinical disease and of the remaining 34 only 26 have been followed for 5 years. The 34 cases represent 3 per cent of the clinical lesions.

Table I shows "5 year survivals" in the various International stages. It is realized that now only cases up to the year 1954 may be included.

The high survival rate in Stage 0 and the low rate in Stage IV are obvious. Actually the one patient who was not a survivor in Stage O died of other causes. Stage I includes 88 preclinical cases.

Fig. 3 shows an individual age-stage correlation which indicates a distinctive trend

Table I. Five-year survival rates according to stage

Stage	*No. cases*	*5 year survival*	
		No.	*%*
0	51	50	98.0
I	407	291	71.5
II	333	134	40.2
III	210	38	18.1
IV	60	1	1.1

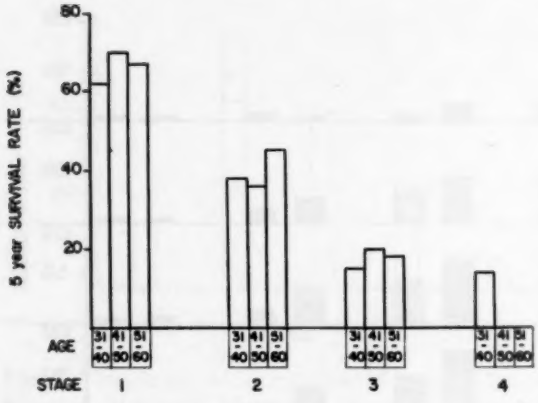

Fig. 4. Percentage 5 year survival by age and stage.

toward a higher stage with advancing age. This may be explained partly by the tendency of younger women to seek screening procedures and by older women to disregard symptoms. It is noted that the highest incidence of carcinoma in situ is in the 31 to 40 age group whereas for Stage I it is in the 41 to 50 group. If Stage I is divided into preclinical and clinical lesions then the age group of highest incidence of carcinoma in situ is 31 to 35, that for preclinical Stage I is 35 to 40, and that for Stage I clinical is 46 to 50. These figures correspond closely with those in reports by Wheeler and Hertig[9] in 1955, by Latour and Brown[4] in 1957, and by Stern[6] in 1959.

Fig. 4 shows the percentage age-stage survival rate of the three major decades of the series. The number of cases at either end of the age scale is relatively very small and these cases have been excluded. All the preclinical cases have been removed and the series is now reduced to 773. The cure rate in Stage IV is so small that to all intents and purposes this stage might as well not be considered. The difference in the percentage survival rate in Stages I, II, and III for the three age groups is very small, the actual figures being 62.2, 70.5, and 67 per cent for Stage I, 38.3, 36.1, and 45.1 per cent for Stage II, and 15.4, 20, and 18.9 per cent for Stage III. However, the slight difference seems to indicate a poorer prognosis for the younger woman. Lindell's[5] tables showed percentages of 65.5, 67.9, and 67 per cent for Stage I, 49, 40, and 48.1 per cent for Stage II, and 12.8, 19.5, and 24.2 per cent for Stage III. Corresponding figures from Truelsen's[8] tables show 59.3, 61.7, and 70.1 per cent for Stage I, 37.2, 39.5, and 44.8 per cent for Stage II, and 13.2, 22.8, and 22.4 per cent for Stage III.

Truelsen reported 59 patients under the age of 30 in Stages I, II, and III. The survival was 59.1, 38.9, and 15.8 per cent, respectively. Lindell, with a much larger series, reported corresponding figures of 54.3, 40.3, and 8.2 per cent. In this series there were only 26 patients under the age of 30.

Summary and conclusions

1. This material shows a distinct bias in the direction of more advanced stages with increasing age. The most obvious finding in this regard is that preclinical cancers antedate the clinical cancers by some 10 years.

2. The age-stage survival analysis does not permit firm conclusions. If there is any difference it is in the direction of the younger women having a poorer prognosis, but this difference is slight.

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Prognosis in carcinoma of the cervix as determined by vaginal smear

A further report

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THE uncertainty of prognosis following therapy for cancer of the cervix is commonly explained on the basis of clinical and histologic differences.[1] This presentation is confined to the cytologic differences before and during radiotherapy as a method of estimating prognosis. A preliminary report[2] was presented to this Society at the Ninth Annual Meeting in 1953, when we stated that our equivocal results justified further study of more patients. It seemed fitting that our further report should be presented to this Society.

In 1947 Graham[3] described changes in the benign cells of the vaginal smears during irradiation for carcinoma of the cervix. The changes were an increase in cell size, vacuolization of cytoplasm, and bizarre nuclear changes. This radiation reaction or RR was recorded on a percentage basis after 100 consecutive superficial and basal type cells were observed.

Following as small a dose as 1,000 r, Graham claimed to observe differences in patients' RR of prognostic value. More than 75 per cent RR indicated a good prognosis following radiotherapy, but less than 65 per cent RR was a poor sign. The 5 year survival published in 1953[4] was 59 per cent for the good RR cases and was only 3 per cent for the poor RR group. Nielsen[5] supported the claims for RR prognosis in a preliminary report. Maloney[6] in our clinic saw no RR differences but claimed that the persistence of malignant cells in smears beyond the twentieth day of high voltage therapy carried a poor prognosis. In the same period, we presented our preliminary report[2] on the prognostic value of RR. Graham's claim for RR early in therapy could not be confirmed by us, but significant results were obtained when RR was studied further along in high voltage therapy. As previously reported by Maloney,[6] the persistence of malignant cells beyond the third week of high voltage therapy precluded any good RR which the patient might possess.

As a further refinement of prognostic acumen, Graham and Graham[7] in 1953 described their sensitization response or SR seen in basal type cells before therapy. SR was recognized as a fine vacuolization, red granules, and violet staining in the cytoplasm of the basal vaginal cell. As much as 10 per cent SR was good and gave a 5 year survival of 66 per cent, but less than 10 per cent SR was poor and gave only an 18 per cent 5 year survival following radiotherapy. Further studies by Graham and Graham[8-10] have supported the original claim for the SR sign.

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Presented at the Sixteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Jasper, Alberta, June 10-12, 1960.

Fig. 1. Basal type cell (BT) of the vaginal smear demonstrates sensitization response (SR) seen in some cells prior to therapy. (Original magnification ×1,344.)

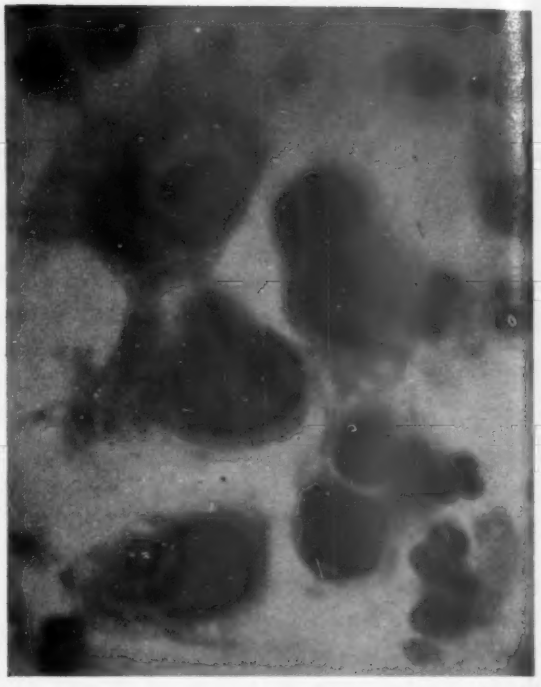

Fig. 2. Malignant cells seen in the vaginal smear after the third week of high voltage therapy indicating a poor prognosis in a high percentage of radiated patients. (Original magnification ×1,344.)

Because of the equivocal results in our experience with the RR and SR signs, we were determined to pursue these cytologic prognostic studies before allowing them to influence our therapy.

Procedure

Vaginal smears were taken weekly and more often during therapy. The Papanicolaou method of preparation and staining was used. The technician was trained as a screener with the advantage of further training as a screener by Graham in her laboratory in Boston and later in Buffalo.

Patients with Stage I carcinoma of the cervix received radium therapy first during the initial 2 weeks; after 4 weeks' rest, they received 400 kv. therapy daily to one of 6 external ports for 5 weeks. This sequence was reversed in the cases of Stage II disease. The sequence has remained unchanged in these stages except for the substitution of cobalt bomb therapy for 400 kv. therapy in recent years.

All patients with too few smears have been excluded from the study, which makes this a selected series. This mode of selection is considered desirable in this instance where we are testing the accuracy of a test. The smear results were unknown to the radiotherapists and to the consulting staff.

We estimated the need of a series of at least 250 cases of Stage I and Stage II disease with 5 year follow-up in order to reach a final conclusion on the value of smears for prognosis. Accordingly, the following results are reported.

Results

Typical pictures of the vaginal smear before and during therapy have been previously published.[2] To these 2 photomicrographs illustrating particular problems are added Figs. 1 and 2.

Our present results for RR after the major portion of radiotherapy are shown in Table I. One notices the division of Stage II into IIa and IIb, which requires some explanation. Stage II (WHO) in our clinic is divided into a and b to separate the early

lesions from those with quite marked extensions. A case of Stage IIa is usually one with visable spread to fornices but without palpable disease in the broad ligaments or other tissues beyond the uterus. Table I shows the results of follow-up 5 years after initial treatment of 272 selected cases of Stage I and Stage II disease. One notes that a good RR is more common. The gross survival was 54.7 per cent in the good RR group and 40.8 per cent in the poor RR group. The net figures are fairer to the RR test, because all cases of death except by cancer are removed from the series. If one further adjustment is made, namely, the exclusion of all deaths except in those patients with persistent disease in the pelvis, the net results are as shown in Table II. In this series of 222 cases including only deaths of patients with pelvic disease, the difference in survival in the two response groups is more significant, namely, 68.5 per cent for the group with good RR and only 45.5 per cent for the poor RR group.

Table III deals with SR and gross survival. One notes that an opposite situation to that of the RR tables does exist. The patient with poor SR is more common. Differences in survival in the two groups are lacking. The net results shown in Table IV are achieved by the same process of adjustment as that employed for the RR results in Table II. Although there is an apparent difference in the net results in the two SR groups, statistical significance is lacking.

Table V deals with our present experience

Table I. Radiation response (RR) and 5 year survival

Stage of disease	*Total No.*	*Good response group*			*Poor response group*		
			Survival			*Survival*	
		Group No.	*No.*	*%*	*Group No.*	*No.*	*%*
I	167	132	85	64.4	35	17	48.6
IIa	81	69	28	40.6	12	3	25.0
IIb	24	22	9	40.9	2	0	0.
Total	272	223	122	54.7	49	20	40.8

Table II. Radiation response (RR) and net 5 year survival

Stage of disease	*Total No.*	*Good response group*			*Poor response group*		
			Survival			*Survival*	
		Group No.	*No.*	*%*	*Group No.*	*No.*	*%*
I	133	103	85	82.5	30	17	56.7
IIa	68	56	28	50.0	12	3	25.0
IIb	21	19	9	47.4	2	0	0.
Total	222	178	122	68.5	44	20	45.5

Table III. Sensitization response (SR) and 5 year survival

Stage of disease	*Total No.*	*Good response group*			*Poor response group*		
			Survival			*Survival*	
		Group No.	*No.*	*%*	*Group No.*	*No.*	*%*
I	112	38	22	57.9	74	45	60.8
IIa	42	10	3	30.0	32	6	18.8
IIb	28	11	1	9.1	17	6	35.3
Total	182	59	26	44.1	123	57	46.3

Table IV. Sensitization response (SR) and net 5 year survival

Stage of disease	Total No.	Good response group			Poor response group		
			Survival			Survival	
		Group No.	No.	%	Group No.	No.	%
I	89	25	22	88.0	64	45	70.3
IIa	34	7	3	42.9	27	6	22.2
IIb	26	10	1	10.0	16	6	37.5
Total	149	42	26	61.9	107	57	53.3

with survival and persistence of malignant cells in the smears after the third week of high voltage or cobalt external pelvic therapy. One notes that the diagnosis is not made often in the face of many bizarre changes seen in smears of irradiated cases; but, of 25 cases so diagnosed, there were 16 in which death resulted from persistent pelvic cancer.

Comment

We have carried out this experiment according to our facilities. The special training of the cytology screener was very desirable but it may be an error to overlook other human factors. A shortage of hospital beds makes it difficult to obtain more than one or two pretreatment smears for SR study of a patient. Furthermore, well-prepared smears naturally increase accuracy, and the best ones are prepared by the cytology staff.

Those who have had similarly poor experience with SR might ponder their routines and facilities, as we have done, before discarding this difficult test.

Conclusions

1. A selected series of patients treated by radiotherapy for Stage I and Stage II carcinoma of cervix is presented with a comparison of cytologic prognosis and subsequent clinical course.

2. The value of radiation response or RR sign of Graham is partially recognized, bearing in mind that significant differences are seldom noted by us until the patients have received almost complete therapy. Our failure to find value in RR after only initial therapy cannot be explained on differences in routine or technique.

3. The value of sensitization response or SR sign of Graham and Graham is equivocal in our hands. Certain differences in routine beyond our control may be responsible. We are again reminded of the general advantage of a preliminary period of investigation and preparation in the hospital before therapy is planned and instituted.

4. We agree with Maloney that persistence of malignant cells in smears beyond the third week of external pelvic therapy carries a poor prognosis.

5. We would recommend the use of cytology in the investigative routine of cases of carcinoma of cervix, bearing in mind its limitations in our hands. The final decision of type of treatment or retreatment must rest with the gynecologic surgeon and the radiotherapist, with all possible clinical and laboratory information at their disposal.

Table V. Carcinoma of cervix (Stages I and II)

	Alive	Dead
A. Persistent malignant cells and 5 year survival	6	19
B. Persistent malignant cells and net 5 year survival	5	16

I am grateful for the generosity of The Ontario Cancer Treatment and Research Foundation and of the fund of the late J. P. Mitchell. The assistance of Drs. D. E. Cannell, W. G. Cosbie, C. L. Ash, T. C. Brown, and A. J. Phillips is remembered. The cooperation of Dr. R. M. Graham and Dr. J. B. Graham was unfailing. The efforts of Mrs. Shirley Gordon and Miss Mabel Clark are appreciated.

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Radiation therapy for carcinoma of the cervix

A report of 145 cases

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DESPITE extensive research and increasing clinical experience, cancer still remains one of the major problems confronting the medical profession today. Reviews of this subject, by several authors, paint a dismal picture regarding scientific accomplishment. May one be so bold as to cast a glimmer of optimism on this dark scene? This hopeful thought is based on the results being obtained in the treatment of carcinoma of the cervix. It appears that, except for skin cancer, carcinoma of the cervix offers the woman affected with this disease the best chance of survival. Although treatment of this condition leaves much to be desired, improved radiation techniques and surgical procedures have achieved excellent results, particularly in the early stages of the disease. The continued publicity given cancer has undoubtedly educated (or frightened) many patients to consult doctors early, and so cases of early carcinoma present themselves more often. This fact will probably improve the results already obtained.

Meigs and others who have sponsored the surgical approach to this problem in recent years, present excellent results in Stages I and II. In Stage I, Meigs[1] has reported 84 per cent 5 year survival and, in Stage II, 58 per cent. Schmitz and Smith[2] present encouraging statistics which show the result of radiotherapy measures (Table I). In both instances, primary complete therapy is most effective in Stages I and II.

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Presented at the Sixteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Jasper, Alberta, June 10-12, 1960.

Mode of therapy

This report will deal with the results obtained in 145 patients whose treatment and follow-up began in 1952, 1953, and 1954 at the Saint John General Hospital, Saint John, New Brunswick. The statistical tables will show that the results in the early stages follow the pattern set by other centers. Here it is felt that the more conservative method of treatment is the one of choice and is less fraught with serious complications. As far as the surgical method is concerned, it is suggested that radical operations be performed only at those centers where extensive surgical experience is available and then only by specially trained gynecologists.

Centralization of cases, as demonstrated by the system used in the Province of New Brunswick, has not only improved treatment measures but also has increased the knowledge and broadened the experience of those administering the treatment. Greater control of the patients has been made possible, and follow-up examinations are more complete. Some patients are directly referred to this center from physicians in private practice, but most sufferers from carcinoma of the cervix come from cancer clinics. These clinics are established at key points in the province, where diagnosis is made. Once diagnosis is confirmed, the patients are sent to Saint John for radiation therapy.

At the hospital, the patients are seen and

examined conjointly by the gynecologist and radiotherapist. Extent of the disease is determined and the method of approach agreed upon. Usually radium insertion is first performed and this is followed by x-ray or cobalt teletherapy. If, however, the tumor has distorted the cervical anatomy so as to make it impossible for the cervical canal to be found, deep therapy is first tried. Radium will later be inserted with relative facility to complete treatment. Regardless of the extent of the disease, the same maximum dosage, calculated to reach the affected areas, is used.

In order to apply adequate radiation properly, patients are x-rayed after radium insertion to determine the location of the radium. Anteroposterior and lateral views are taken. This aids in locating the portals for administering deep therapy. It was the aim to deliver a total dose by radium of 7,000 r (6,800 rads) at Point A and 1,500 r (1,450 rads) at Point B; and, by means of x-ray or cobalt teletherapy, a dose of 2,000 or 2,250 r, respectively, is given within the next 2 weeks to the lateral portions of the parametrium. Most patients remained in hospital throughout the period of treatment. A few local residents were permitted to be treated as outpatients in the later stages of deep therapy.

Results

The statistical summary of the results of treatment is shown in Tables II and III. The figures shown in the tables include all cases completely and partially treated. All deaths, regardless of cause, are included as cancer deaths. The percentages stated are the nearest whole number.

Complications of treatment

During the period of active treatment, the most frequent complication is diarrhea due to proctitis. This problem usually resolves itself spontaneously in most cases shortly after treatment ceases. Several cases, however, require special attention. Retention starch enemas appear to give quick relief. Vomiting or anorexia is another feature.

Table I. Report of cases treated by Schmitz and Smith[2]

Stage	*No. cases*	*Living 5 years*	*Percentage*
I	37	32	86.5
II	82	53	64.6
III	141	58	41.1
IV	80	8	10.0
Total survival			44.4

Table II. Five-year survival

Year	*No. of cases*	*Living at end of 5 years*	*Percentage*
1952	48	33	69
1953	57	36	63
1954	40	25	63
Total	145	94	65

Table III. Breakdown in stages

	Cases	*5 year survival*	*Percentage*
Stage I	37	34	92
Stage II	47	37	79
Stage III	48	22	46
Stage IV	13	1	8

Antiemetic drugs were usually helpful. Frequency of micturition sometimes occurred.

Later complications or sequelae were remarkably few, and the number increased in proportion to the extent of the disease before treatment was instituted. Rectal complications totaled 5.9 per cent. These were bleeding, strictures, ulcerations, and telangiectasis. Of these only 1.1 per cent remained really troublesome.

Vaginal complications were usually those of atresia, and in some cases colpocleisis. The practice of early coitus prevented this condition in some cases. Vaginal bleeding was encountered in 4.3 per cent, but this ceased after several months. Hematuria, due to bladder ulcerations or telangiectasis, occurred in 5 per cent. This complication subsided gradually in 2 years or more. There was one case of skin necrosis, one vesicovaginal fistula, and one case of lymphedema of one leg.

Conclusions

The conclusions one can draw from this dissertation is that treatment of carcinoma of the cervix by radiotherapy can be very effective, but this fact depends on the following criteria:

1. Treatment must be administered in the early stages of the disease.

2. Teamwork is essential, and this involves the close and speedy cooperation of the diagnostician, the gynecologist, and the radiotherapist.

3. Adequate facilities for complete treatment.

4. A good system of following the progress of the patient.

Conscientious reporting is also essential in evaluating results. Making allowances for one thing or another is only a mask which misinforms those persons concerned with the program and may lead to false conclusions. It is hoped that with the extensive research that is constantly being carried on in this field the ideal goal of specific therapy for this devastating disease will someday spark a new era in medical achievement.

This report is based on the combined efforts of treatment by the Departments of Gynecology and Radiotherapy of the Saint John General Hospital. Grateful thanks are extended to Dr. J. A. Caskey, particularly, and Dr. D. Smith of the Radiotherapy Department, and Drs. G. M. White, F. D. Wanamaker, D. F. Sutherland, and T. A. Foster of the Department of Gynecology.

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Factors affecting the prognosis of cancer of the cervix in pregnancy

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A BRIEF survey of the recent American and British literature reveals that cancer of the cervix in pregnancy is still rare. Of fifteen papers reviewed,[1-14] only four[1, 2, 3, 6] reported more than 15 cases and many of the other eleven reported very few cases with a follow-up of 5 years. As a result, there is, as yet, no agreed method of treating cancer of the cervix in pregnancy. On the bright side, there is a great resurgence of interest in the earlier diagnosis by exfoliative cytologic techniques of the Stage 0 lesion in pregnancy.[15-17] There is increasing faith in this method as a useful screening procedure during pregnancy. There is a rapidly dying impression that the Stage 0 lesion as diagnosed during pregnancy is an evanescent situation.

No attempt has been made to include the Stage 0 lesion in this survey. Indeed, only 3 of these were diagnosed in the period of this study. It is hoped that this analysis will serve as a base line for subsequent surveys. It is hoped that future surveys will be able to concentrate mainly on Stage 0 lesions and that the therapeutic results obtained in this survey will be quickly rendered obsolete.

Materials and methods

Through the courtesy of the Ontario Cancer Foundation, 105 cases of cancer of the cervix diagnosed during pregnancy, or within the first 6 months post partum, have been analysed. Of these cases, 68 were from Toronto, 21 from London, 6 from Ottawa, 4 from Hamilton, 4 from Kingston, and one each from Thunder Bay and Windsor. The period covered was from 1933 to 1953, inclusive—although 30 of the cases analysed were diagnosed after 1953. In order to present only those cases with a follow-up of 5 years or more, this latter group was excluded, leaving a final total of 75 cases. One hundred and seven cases in which cervical cancer was diagnosed before the age of 35 in the nonpregnant woman were analysed from the London Clinic. The Ontario Cancer Foundation supplied the statistics of 402 patients under the age of 35. All had been followed for 5 years or more.

Effect of pregnancy on prognosis

A comparison of the 75 pregnant patients with 402 patients in the comparable age group of 35 years or under shows an almost identical 5 year survival rate of 44 per cent as compared with 45 per cent (Table I). This must be compared with a survival rate of 41 per cent in an all-inclusive group as reported by Sellers and MacKay.[18] The conclusion is that there is no general worsening of the prognosis when this lesion is complicated by pregnancy.

Effect of stage of lesion

It will be seen that the survival rate of 64 per cent in Stage I cases of the pregnancy series is almost identical with that in the

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Table I. Effect of stage on survival

Stage	Cases	Alive 5 years		Cases	Alive 5 years	
		No.	%		No.	%
I	28	18	64	147	100	68
II	23	12	48	155	61	40
III	14	2	14	88	16	18
IV	10	1		12	1	
Total	75	33	44	402	178	45

Table II. Percentage of cases in each stage

Stage	Pregnant		Nonpregnant under 35	
	No.	%	No.	%
I	28	37.4	147	36.8
II	23	30.4	155	38.8
III	14	18.4	88	21.8
IV	10	13.8	12	2.6
Total	75		402	

comparable nonpregnancy series. The figure agrees closely with that of 66 per cent quoted by Sadugor and associates,[1] who compared findings in 48 pregnant patients with those in 709 patients between 20 and 45 years of age. This group reported a 5 year survival rate in Stage I of 68 per cent. Again, in a comparable age group, pregnancy made no difference to the prognosis by stage.

The stage of the lesion is, however, a very important factor in the ultimate prognosis. In the present series 37.4 per cent of the patients were in Stage I (Table II). This compares favorably with the 24.3 per cent of patients in Stage I in the entire Ontario Cancer Foundation series. It is obvious that far too few lesions are diagnosed in the early stages.

Effect of trimester in which the lesion was diagnosed

The observations are too few to make any definite statement. Certain trends may be recognized (Table III). Forty-nine of 75 cases were diagnosed during labor or in the postpartum period. It is at these times that the cervix will either give the obstetrician concern as in labor or come under close *routine* scrutiny at the postpartum examination.

Only 16 cases were diagnosed in the second or third trimester. This illustrates the reluctance of the physician to inspect, let alone palpate, the cervix in the case of bleeding in these trimesters. This may cause tragic delay in diagnosis. This is emphasized in every paper on this subject and it only remains to reiterate that *any* bleeding at *any* time during pregnancy must be dealt with by inspection of the cervix and cytologic examination.

Parenthetically, it should be pointed out that in 2 of these cases cesarean section was carried out for placenta previa and the real lesion was diagnosed only at the postpartum examination.

There is a slightly higher survival rate in those cases diagnosed before labor compared to those diagnosed during labor or early in the postpartum period. That poor results follow diagnosis in the postpartum period is supported very strongly by Bickenbach and Soost,[19] Jones and Neill,[4] and Maino and Mussey.[3] This is not so obvious in the present series, although such a trend is apparent, particularly in the Stage I and Stage II lesion.

Table III. Effect on survival of trimester in which the cancer was diagnosed

Trimester	Stage				Total	5 year survival	
	I	II	III	IV			
First	5	4	1	0	10	6/10	15/26
Second	3	3	3	1	10	5/10	
Third	2	3	0	1	6	4/6	
Labor	2	3	4	3	12	4/12	18/49
Post partum	16	10	6	5	37	14/37	
Total	28	23	14	10	75		

Prognosis in Stage I cases

The stimulus to begin this study came from observation of 3 cases, diagnosed clinically as Stage I in pregnancy, in which the patient died with generalized metastases within one year. Accordingly, all Stage I lesions were analysed up to 1956. This gave 42 cases of Stage I, with a 2 year follow-up in this series. They were then compared with 46 cases in nonpregnant patients under 35 years of age.

In the pregnant group, 13 of the 42 were dead within 2 years, but, in the nonpregnant group only 5 of the 46 died in that length of time. The results in the nonpregnant group were obtained from an anlysis of 107 cases of cancer of the cervix occurring in nonpregnant women in the age group under 35 recorded in the files of the Ontario Cancer Foundation, London Clinic. This difference is statistically significant.

Of the pregnant patients, 6 developed generalized metastases and pulmonary metastases and 4 had massive pelvi-abdominal metastases (Table IV). In the nonpregnant group, 3 had widespread metastatic disease (Table V). The same rapid deterioration is apparent in both groups, although proportionately this occurred more frequently in the pregnant group.

When the trimester in which the diagnosis is made is considered, the same trend appears. No cases were diagnosed in the second and third trimesters, 11 were diagnosed during labor or in the postpartum period (Table VI). Nine of these patients were delivered vaginally and one by cesarean section (Table VI). It is obvious that in this age group, even when the cancer appears clinically to be in an early stage, there may be rapid dissemination of the disease, particularly during pregnancy. The predisposing factors to the rapid spread in pregnancy seem to be late diagnosis and the effects of vaginal delivery. A plea is made again for early diagnosis of early lesions early in pregnancy and for treatment which avoids vaginal delivery. There appears to be no effect on prognosis as far as different treatments are concerned. All but one patient were considered to have been treated adequately (Table VII).

Table IV. Causes of death (within 2 years) in pregnant patients with Stage I lesions

Generalized metastases	3
Pulmonary metastases	3
Massive pelvic metastases	4
Postoperative vault recurrence	1
Died of disease (not stated)	2

Table V. Causes of death (within 2 years) in nonpregnant patients under age 35 with Stage I lesions

Abdominopelvic metastasis	1
Pulmonary metastasis	1
Para-aortic, liver, dura mater	1
Local recurrence	2

Table VI. Trimester at diagnosis and method of delivery of pregnant patients* with Stage I lesions (dead within 2 years)

Trimester diagnosed	
First	2
Second	0
Third	0
Labor	4
Post partum	7
Delivery	
Vaginal	9
Cesarean section	1

*Mean age 31.3; mean parity vi.

Table VII. Method of treatment of pregnant patients with Stage I lesions (dead in 2 years)

Adequate radiotherapy	6
Adequate operation	5
Vaginal hysterectomy and deep x-ray therapy	1
Inadequate operation	1

Table VIII. Average age of marriage

Canada 1957	
Mean	24.2 years
Median	21.8 years
Cancer of the cervix 332 patients	20.8 years
Cancer of the cervix in pregnancy	18 years

Effect of age at marriage and age and parity at onset of disease

There has recently been much speculation as to whether or not age at first intercourse has a definite effect on the etiology and prognosis of this disease.[20, 21] An attempt was made to discover the age of marriage, which we hoped might indicate the age of first intercourse. This information was obtained in 44 cases. In the current series, the average age of marriage was 18 years. McCormick[22] found that the average age of marriage of 332 patients with cancer of the cervix was 20.8 years. The average age of marriage in Canada in 1957 was 24.2 years and the median age of marriage 21.8 years. The average age at diagnosis of cervical cancer in this group was 31.3 years (Table VIII). The average parity was 5.5 compared to 3.6 in the general group. In fact, these patients lived up to the statement of Gower-Jones and associates: "Rapid maturation sexually and a haste to begin early and early to terminate the reproductive phase of biological destiny—marriage, intercourse, first and last pregnancies, separation and divorce—all of these events occur significantly earlier in life of the woman destined to develop cancer of the cervix."[21] These many factors do not seem to have any effect on the ultimate survival. They do, however, provide the physician with an index for suspicion.

Effect of method of delivery

This is demonstrated in Table IX. Many of the patients had undergone delivery before diagnosis. Those cases in Stage I in which there was rapid deterioration pointed to the possible danger that vaginal delivery might produce rapid dissemination of the cancer. The poor results following cesarean section are attributed to the fact that this operation was carried out for obstetric reasons and rarely because cancer of the cervix had been diagnosed. This operation therefore appears in an unfavorable light.

Table IX. Effect of method of delivery on survival rate

Method	*No. patients*	*Alive 5 years*
Vaginal delivery	53	22
Cesarean section	10	2
Abortion	8	5
Hysterectomy, unopened uterus	4	4

Effect of treatment

In general, in this series, irradiation was the main basis of treatment. The ultimate result compares favorably with the generally quoted 5 year survival rate for this disease (Table X). As in every series, there are freaks. The success of inadequate operation followed by irradiation gives cause for concern. Nolan,[23] reporting 38 similar cases, states that radiation therapy in such situations is definitely limited in its effectiveness, and the chances of salvage are slight. None of his patients were pregnant.

Conclusions

It is very difficult to be dogmatic about the treatment of these patients. The same controversy exists as with the nonpregnant patients. The presence of a fetus influences treatment specifically but there seem to be certain general ground rules which can be laid down as a guide to therapy.

1. The earlier the stage, the earlier during pregnancy the disease is diagnosed, and the earlier it is treated the better the result.

2. From unfortunate experiences with certain Stage I cases, it is suggested that vaginal delivery with concomitant cervical trauma may produce rapid dissemination of the disease.

3. The worst results occurred in cases diagnosed and treated just after labor and in the postpartum period.

4. In a selected few, radical hysterectomy on the unopened uterus may give good results.

From these observations, a course of treatment can be outlined. There is no dispute about the postpartum cases. These patients should be treated exactly as if they had not been pregnant.

Table X. Effect of various modes of treatment*

Stage	5 year survival				
	Adequate radiation	*Adequate operation*	*Operation and radiation*	*Inadequate operation and radiation*	*Palliative radiation*
I	13/19		2/4	3/5	
II	9/19	1/1	1/3	1/1	
III	1/10			1/1	0/3
IV			1/1	0/1	0/8
Total	23/47	1/1	3/8	5/8	0/11

*Five-year survival, 44 per cent.

In early pregnancy, the patients in the late stages should be treated by x-ray or cobalt beam therapy to produce abortion, followed by radium application to make up the cancericidal dose.

In early cases, in early pregnancy, the foregoing management will apply equally satisfactorily but a plea is made for removal of the unopened uterus by radical hysterectomy with lymph node dissection by competent hands.

Late cases diagnosed during labor should be treated by cesarean section followed by adequate radiotherapy. Because of involution, deep x-ray or cobalt beam therapy should be started first.

Early cases diagnosed during labor should be treated in the same way, but, again, good results may be achieved by competent and adequate surgical management following cesarean section.

Diagnosis in the second trimester imposes a heavy responsibility. With the patient's concurrence, the pregnancy can be carried on in order to obtain a fetus capable of surviving. At this time, cesarean section followed by radiotherapy can be carried out. It must be remembered that the longer one temporizes, the worse the prognosis for the patient becomes.

Comment

This analysis bears out classical animal studies which showed that pregnancy does not increase tumor growth.[24] These studies pointed out that the pregnant animal could not support both the fetus and the tumor. The fetus thrived, the tumor starved. Put more specifically, this study shows that the prognosis of cancer of the cervix in pregnancy is no worse than cancer of the cervix in the nonpregnant individual in a similar age group.

What influences prognosis? Three factors: early diagnosis, early staging, and early treatment. Again, there is no difference from any cancer of the cervix in the nonpregnant woman. Physician delay is particularly noticeable in the first trimester for fear of disturbing a threatened abortion, and in the second and third trimester for fear of disturbing placenta previa. Thirty-seven of these cases were diagnosed post partum or following dilatation and curettage for an incomplete abortion.

It is obvious that we must be particularly attentive to the postpartum cervix. Also, the ease of obtaining cervical biopsies at dilatation and curettage for an incomplete abortion would strongly support the suggestion that this procedure be adopted as routine.

However, there is one great difference about these patients—they must come to the physician for diagnosis of the pregnancy. They are presenting us with a golden opportunity for early diagnosis of cancer of the cervix and we are not taking it, we may be, in fact, actively neglecting it.

The spectre of the cost of cytologic screening is always raised. A recent report by Banting[25] has shown that at the Women's College Well Woman Clinic, Toronto, it costs about $4,000 to detect an asymptomatic cancer. She rightly concludes that this is not the right approach to the detection of early cancer. However, $4,000 per cancer is

also the wrong approach. In our specialty, this is 800 women paying $5 each to discover one cancer.

The second objection is against routine screening. This study points the finger at those who *must* be screened. These are women who marry at 18 and have 5 children by the time they are 25 to 30 years old.

Preventive medicine is less rewarding and less exciting than curative medicine. At the time of the introduction of routine mass radiography for detection of early pulmonary tuberculosis, there was a hard core of opposition on the grounds that early cases of tuberculosis could be detected by the clinical method of inspection, palpation, percussion, and auscultation. Tuberculosis is now a decreasing disease. Some of the credit for this must go to early radiologic diagnosis. Is it possible that opposition to routine cytology studies may be based on this same attitude that adequate inspection and palpation will diagnose all cancers of the cervix? By all means, let us not stop inspecting every cervix, but let us admit that inspection will not detect the precancerous lesion. Let us enthusiastically support this simple inexpensive screen which may help in exterminating this disease and, in the narrower context of pregnancy, save the life of an otherwise healthy woman.

Summary

This paper analyses 75 cases of cancer of the cervix associated with pregnancy gathered from the records of the Ontario Cancer Foundation from the years 1933 to 1953, inclusive. All of these patients have been followed 5 years or more.

1. When this series is compared with that of 402 cases of cancer diagnosed in nonpregnant women under the age of 35, the 5 year survival rate is identical. Therefore, we may conclude that pregnancy has no effect on the prognosis of cancer of the cervix.

2. Very few cases were diagnosed in the second or third trimester. This reflects the reluctance of the physician to inspect the cervix at this time and the resultant delay in diagnosis. It is emphasized that *any* bleeding at *any* time during the pregnancy demands inspection and cytologic examination of the cervix.

3. There is statistically significant evidence of rapid deterioration and death from widespread metastases in the Stage I lesion.

4. This study indicates those women in whom cytologic screening during pregnancy is mandatory.

5. Routine cervical biopsy is recommended at curettage for incomplete abortion.

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17-Hydroxycorticosteroid levels in pregnancy

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SINCE Venning[1] in 1946 first reported the finding of elevated glucocorticoids in the urine of pregnant women, there has been an increasing interest in the chemistry and metabolism of the adrenal steroids in pregnancy. Within the past decade there have been marked improvements in chemical assay techniques which have rendered possible a new understanding of the individual adrenal steroids. The 17-hydroxycorticosteroids have received particular attention, and the results of many studies are now available in the literature.[2, 3] All studies employing assays for plasma concentrations of free hydrocortisone indicate a progressive rise throughout the course of pregnancy, with a maximum level being reached at the end of the third trimester. A further rise occurs during labor, with an even higher level achieved at delivery. There is a gradual decline in the elevated level until prepregnancy concentrations are reached at the end of the first week.

There is evidence[4] that more complex metabolic changes occur in pregnancy than are suggested by mere elevations in circulating blood levels of individual steroids or groups of steroids. The pregnant patient has been shown to be more sensitive to ACTH stimulation than the nonpregnant patient. This observation plus the recognized evidence for decreased glucose tolerance and the amelioration of such diseases as rheumatoid arthritis and asthma during pregnancy have suggested the existence of "a hyperadrenal state during pregnancy."[4] The fact that the pregnant woman does not exhibit clear-cut clinical evidence of hyperadrenocorticalism as is seen in Cushing's disease, despite the observed high levels of 17-hydroxycorticosteroids, suggests the possibility that in pregnancy adrenocortical steroids may be inhibited in some way from exerting their full biological effects. These and other observations indicate the need for continuing research in this field before any complete understanding of the endocrine interrelationships of pregnancy can be achieved.

One of many promising avenues for study in the pregnant patient is the relationship between the altered metabolism of 17-hydroxycorticosteroids and antibody formation. There is much experimental work in animals to indicate that ACTH and cortisone suppress the formation of circulating antibodies.[5] Unfortunately, so little is known about the biochemistry of antibody formation or the mechanism of action of adrenal hormones that a satisfactory explanation of these antibody-antigen-steroid relationships is not available. The further problem of varying characteristics of differing antibodies, as well as the traditional enigma of species variation, renders the interpretation of data in the experimental animal most difficult.

The therapeutic application of cortisone

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and hydrocortisone in the pregnant patient did not wait for the elucidation of the underlying physiology. Although cortisone and hydrocortisone have been employed moderately extensively in the management of a variety of obstetrical complications which have included nausea and vomiting of the first trimester and toxemia of late pregnancy, the most active application has been in the management of the isoimmunized Rh-negative woman. In general, these therapeutic attempts have proved disappointing, and in the past few years there has been a marked reduction in the use of these steroids for therapeutic purposes.[6, 7] This has been based chiefly upon the recognized failure of their purpose and also on an increasing awareness of potential complications to the mother and the fetus.

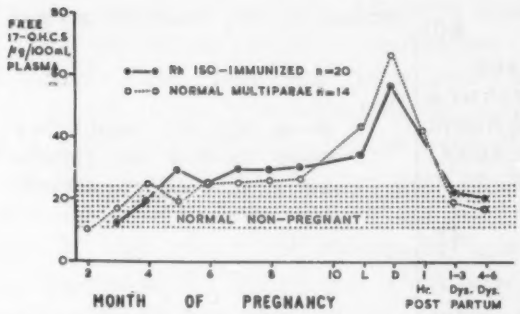

Fig. 1. Porter-Silber chromogens in Rh-isoimmunized and normal multiparas.

Present study

Now that the initial empirical therapeutic attempts have been largely abandoned, it is appropriate that there should be continuing attempts to understand the normal physiology of the immunization-steroid relationship in the pregnant human. A study has been in operation in the Department of Obstetrics in the Vancouver General Hospital in which plasma hydrocortisone levels, as measured by the technique of Porter and Silber,[8] are followed in a group of isoimmunized Rh-negative women, and the values are compared to those in a control group. This study is being carried out with no particular therapeutic application in mind but as a means of observing the relationship of this particular Rh-antigen-antibody system to hydrocortisone levels in the human.

The only similar study that was found in the literature was reported by Gemzell,[9, 10] who restricted his observations to comparisons of values taken at the time of delivery. In a group of 47 unselected normal obstetrical patients the levels of 17-hydroxycorticosteroids following normal labor were found to be significantly higher in primiparas than in multiparas. The reason for this difference is not clear, but it was the opinion of the author that the increased physical and psychic stress of the primigravida accounted for the difference. In 64 Rh-isoimmunized women, all multiparas, the mean concentration of 17-hydroxycorticosteroids (35.5 µg per cent) was higher than that in a control group of nonisoimmunized multiparas (mean, 23.4 µg per cent). Here again the anxiety factor believed to be more

Table I. Mean plasma levels of 17-hydroxycorticosteroids in Rh-isoimmunized mothers during the third trimester and at delivery

	Third trimester		*Delivery*	
Groups	*No. of mothers*	*17-OHCS µg/100 ml. plasma*	*No. of mothers*	*17-OHCS µg/100 ml. plasma*
Baby transfused	9	28.7	11	56.2*
Baby not transfused	6	26.0	7	58.9
Stillborn	2	21.6	2	41.8*
Antibody titer (albumin anti-D)				
< 1:8	11	26.2	11	55.0
> 1:8	5	31.6	9	56.6

*The difference between the delivery level of mothers whose babies were stillborn and those whose babies received transfusions is not significant.

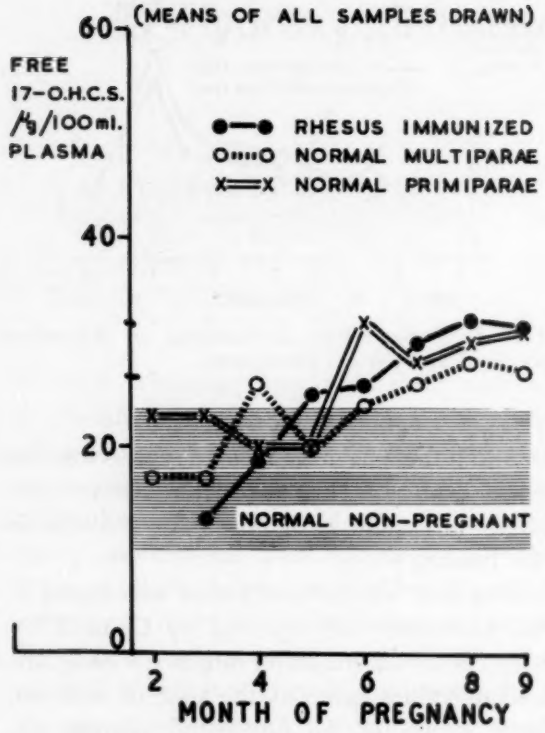

Fig. 2. Porter-Silber chromogens in pregnancy.

marked in the women showing antibodies was used to explain the different values. No relationships between size of infant or duration of labor in immunized and nonimmunized groups could be established.

Material and method

The observations to be reported are based on a study of a group of women, both clinic and private patients, confined in the Vancouver General Hospital. As the problem of isoimmunization involves primarily multiparas, only 6 primiparas were studied in the series. Twenty Rh-isoimmunized multiparas and 14 nonisoimmunized multiparas were followed throughout pregnancy, labor, and delivery (Fig. 1). Samples were collected from an additional 37 immunized and 42 nonisoimmunized women at one or more points in pregnancy or at delivery (Fig. 2). In the cases shown in Fig. 1, blood samples were drawn at monthly intervals throughout pregnancy, during labor, at the time of delivery, and in the first postpartum day. With the exception of labor and delivery samples, blood was collected between the hours of 1 and 3 P.M. in order to reduce the effect of diurnal variation.

The free 17-hydroxycorticosteroids were determined in the plasma from heparinized blood by the Peterson and associates[11] modification of the Porter-Silber[8] method.

Results

1. There is a progressive increase in 17-hydroxycorticosteroid levels with advancing pregnancy, a further rise during labor and delivery, and a prompt decline in the immediate postpartum period (Fig. 1).

2. There is no statistically significant difference in the above patterns between the isoimmunized women and the control group of multiparas. The control group of 14 multiparas had a mean 17-hydroxycorticosteroid level at delivery of 65.9 µg per cent, while the Rh-isoimmunized group of 21 patients had a mean level of only 54.7 µg per cent (Fig. 3). When analyzed statistically, the difference between the means was shown to be insignificant (P lies between 0.05 and 0.1). The marked discrepancy between the reported values of Gemzell and the present study may in part be explained by the

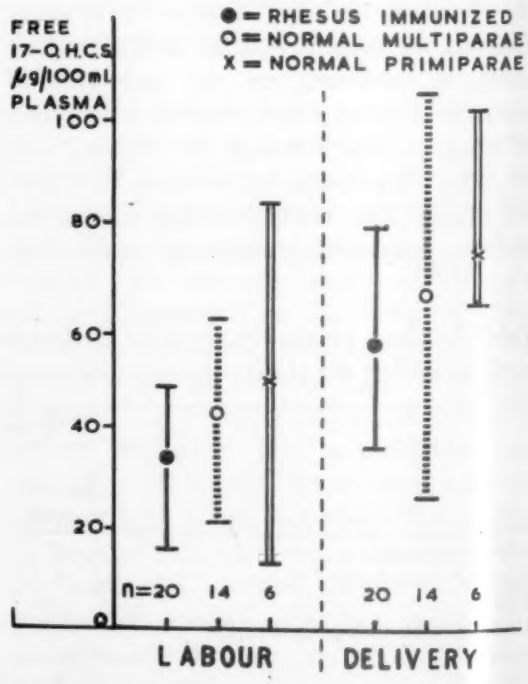

Fig. 3. Range and mean levels of 17-hydroxycorticosteroids in pregnancy.

utilization of different assay techniques in the two series. The assay of Nelson and Samuels[12] was employed in the former study. It has been generally accepted that while the Nelson and Samuels assay and the Porter-Silber technique produce generally corresponding data, the comparison of absolute levels is not justified.

3. As was shown previously, the mean level of 17-hydroxycorticosteroids in primiparas at delivery was higher than in multiparas (Fig. 3).

4. No relationship between the levels of 17-hydroxycorticosteroids and the level of antibody present was noted (Table I).

Comment

The interpretation of data relating to 17-hydroxycorticosteroid levels in the human is always difficult in the light of the known influence of a wide variety of stresses upon adrenal output. Psychic factors in particular represent important forces that are hard to measure objectively and weigh in any assessment of data. Although these factors were implicated in the evaluation of Gemzell's data, there was no evidence in the smaller series here reported that there is a significant difference between the test and the control groups at any stage of the period studied. These observations suggest that in the human the process of isoimmunization to the Rh antigen is not associated with an alteration in the output of 17-hydroxycorticosteroids. This failure to stimulate an increased production of endogenous 17-hydroxycorticosteroids in the healthy isoimmunized pregnant woman may be interpreted as indicating an absence of a significant antigen-antibody complex (Rh) in the human. It may also explain the therapeutic failures which have been observed when cortisone has been administered to the pregnant woman to prevent isoimmunization or to reduce antibody titers and protect the unborn fetus.[6, 7]

The technical assistance of Miss Lubinka Kujovich is gratefully acknowledged.

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GYNECOLOGY

The natural history of cancer of the cervix

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The terminal picture gives the key to the partially revealed processes during life.
Archibald Leitch

MY TOPIC is "The Natural History of Cancer of the Cervix" as disclosed by autopsies performed before the era of definitive treatment with radium and/or surgery. *Mortui vivos docent.** I have selected Archibald Leitch's[1, 10, 11] observations on 2,111 cases as the basis of these remarks. They were accumulated from 1855 to 1904. His observations made over 50 years ago are as good now as they were then, showing how slowly we have added to our knowledge of the pathology of cervical cancer.

Leitch wrote several papers on the subject in 1910, one with Andriezen[1] while Assistant to the Director of the Cancer Research Laboratories of Middlesex Hospital, London. These were written after abdominal hysterectomy and lymph node dissection had been advocated by Reis[13, 14] of Chicago in 2 papers published in March and November, 1895. The abdominal approach challenged the vaginal operation which was then in vogue.

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**The dead shall teach the living.*

Victor Bonney[2] was the research assistant at Middlesex Hospital at the time Leitch made these studies. This hospital later became the center for the radium treatment of patients with cancer during World War I. Bonney did not operate upon his first patient until 1907 after a visit with Wertheim,[18] who was to become the most formidable of the early operators for uterine cancer both here and abroad.

Reis[15] stated in a third paper, published in 1897, that he had visited Baltimore and had given Kelly a reprint of his paper which had compared the problem of cancer of the cervix spreading to regional nodes with cancer of the breast. He probably developed this concept from Halsted[8] who began radical breast excisions in 1889, or 6 years before Reis published his concept. Reis performed his operation first on cadavers and dogs and, finally, on a living subject in March, 1897. Meanwhile, Rumpf[16] of Berlin first performed this operation in June, 1895. Thereafter, Clark[4, 5] in Baltimore, while still a resident and assisted by Kelly, performed radical hysterectomy and removal of the nodes at the pelvic brim in October, 1895. Kelly did a

similar operation in October, 1895. These patients were also mentioned by Cullen[7] in his textbook.

It appears from careful perusal of the literature that the so-called Wertheim procedure was performed by Rumpf, Clark, Kelly, and Reis long before Wertheim, Bonney, and others. Wertheim's paper on 500 cases was published in 1912. It was translated from German into English by Hermann Grad of Woman's Hospital, which made it more available to the surgeons of this country The early operators had to cope with an operative mortality ranging from 15 to 30 per cent, which was accepted because the patients were doomed anyway.

While Clark was the first in this country to employ radical surgery for cervical cancer, he was also one of the first to stop using it in favor of radium saying with Keene[6] in 1921, "we shall cease to speak of any operable cases of cancer of the cervix but shall submit them all to irradiation."

Leitch's[1, 10] studies were based on 915 necropsies on patients who had died of the disease without treatment. Cervical cancer had spread to the corpus in 613 cases, while 219 had no note on this point, and in 83 or 11 per cent the uterus was not involved, making 915 cases in all. All but 3.5 per cent had spread beyond the cervix.

Leitch found that 55 per cent of 915 patients who died with cervical cancer were free of visceral or lymph node metastases. He said that this accounted for the fairly good results obtained by vaginal hysterectomy. Does it not also account for the cures obtained today by abdominal hysterectomy and/or radium therapy? Such patients have disease limited to the cervix or adjacent structures that are within reach of the operation or the radiation. When the disease has involved the pelvic structures or gone beyond to distant viscera, surgery and radiation are merely palliative. The liver had metastases in 13 per cent of the patients, the lungs in 6 per cent, peritoneum in 5 per cent, suprarenal glands in 2 per cent, heart and spleen in 1 per cent each. These percentages agree with those reported in the literature of the same period. Other scattered metastases were found in lesser percentages.

It is a well-known fact that when the lymph nodes are positive, the disease has often spread to distant viscera, and Wertheim emphasized that under such circumstances the results were poor. Perhaps the greatest value of lymphadenectomy is to establish prognosis, as suggested by Clark[5] and Wertheim.[18] When the nodes are negative, the prognosis is good and they do not need to be removed except to establish that important fact. When they are positive, the prognosis is poor, although Riva[19] and Brunschwig[20] discuss 5 year cure rates in patients with positive nodes. But let us bear in mind that surgical skills vary, and most of us do not cure patients with positive nodes, at least when more than one is positive. The same situation holds true for the breast. It is a well-known pathological fact that positive nodes invariably signify hematogenous metastases as well.

Today autopsies on cases of cancer of the cervix are relatively rare. Current studies consist largely of treated patients and a small number of cases. Many patients die in terminal care hospitals like the House of Calvary, St. Barnabas, or St. Rose in this city, where autopsies are seldom performed. Even at Memorial Hospital over a 30 year period, only 65 necropsies were done between 1917 and 1948 according to Brunschwig and Pierce.[3] Nearly all of these patients had been treated with radiation, and 52 of them still had residual cancer in the cervix, a strong argument for a third school of thought which advocates radium followed by operation; this, however, almost doubles the risk of ureteral complications, that bugbear of both radiation and surgical therapy. Leitch[11] also wrote about the ureteral complications and hydronephrosis as a natural course of events due to the spread of cancer, to infection, or both. Yet today we tend to forget this fact as we blame the radiologist or the surgeon for ureteral fistulas and strictures that are due in part to the ravages of the disease as well as to the therapy. As a pathologist, Leitch advised against stripping the ureters.

Shields Warren[17] of Boston described 132 necropsies in 1933, emphasizing that they represented failures in treatment. Henriksen[9] emphasized in 1950 that there was little difference between the autopsy findings in treated and untreated patients. The New York Gynecological Society, by collecting and studying protocols of a large number of treated patients, could obtain pertinent statistics, especially the gross over-all mortality rate for New York City. This would be very helpful in evaluating the therapy of various hospitals in the city against this figure. We could render a valuable service to our community much as the Academy of Medicine has done for maternal mortality by sponsoring a Committee on Cervical Cancer. We must constantly bear in mind that autopsies will give us the true extent of the disease. However, the next best evaluation is diagnostic exploratory laparotomy and operations on the living with the development of surgical pathology as advocated also by Leitch. Surgery will disclose the extent of the disease and permit its removal, which cannot be accomplished by purveyors of radium who as keyhole surgeons are working in the dark.

Leitch[10] called attention to the area bounded by the bifurcation of the common iliac vessels and the base of the broad ligaments, calling it the "axilla" of the pelvis. Here he found pelvic lymph node metastases in about 45 per cent of the cases. Leitch said that the cervix and uterus have numerous lymph channels that fuse into major trunks on either side, emptying cephalad into the interiliac and aortic nodes, and caudad into the obturator and inguinal nodes. The inguinal nodes were involved in 5 per cent of the cases. He said for practical purposes the lymphatic spread is the same for both cervical and endometrial cancer and that the operation should be the same for both conditions. This view is contained in the literature of the day, when many authors writing on cancer of the uterus did not always distinguish between cervical and uterine cancers. For that matter few authors today carefully distinguish the squamous cancers from the adenocarcinomas of the cervix.

Leitch said that the misleading problem in cervix cancer is the septic absorption with induration of the parametrium and enlargement of the nodes, producing a disagreement as to the clinical and pathologic interpretation. This disagreement has continued to the present day when recent authors have emphasized an average difference between the clinical and pathologic stages of around 33 per cent. Despite the high incidence of parametrial involvement, the ovaries are seldom involved—only once in Warren's cases, and I have seen it only twice in 200 surgical specimens representing all stages of the disease. So it is the base of the broad ligaments rather than the appendages that are involved. He said that it was impossible to determine clinically or at operation the exact extent of the disease, and the more the surgical pathology was understood the more radical the operation would become. How true this prediction has been in the past 20 years with the revival of primary operations for cancer of the cervix.

Vaginal metastases were most frequent and occurred in 97.5 per cent of Leitch's autopsies. Clark also recognized this as did Wertheim, who devised a clamp for removal of the cervix contained in the vaginal cuff. Spread was found anteriorly from the vagina by contiguity to the urinary bladder in 66 per cent of the patients, showing urinary fistulas in 44 per cent. It can be presumed that such spread implied coexisting spread to the ureteral lymph nodes and the ureters since 75 per cent of the patients had hydronephrosis. The majority probably died of uremia, which was Nature's way of putting an end to their pain and suffering.

Spread posteriorly to the rectum occurred in only 25 per cent, with fistulas in 16 per cent, certainly much less frequent than the anterior spread. Even the pararectal nodes are seldom involved, only once in 107 cases studied by MacCormac.[12] Both vaginal and rectal fistulas were found in 9 per cent of patients in a terminal condition. Today about 25 per cent of these patients are rehabilitated by the exenteration procedures pioneered by Brunschwig.

Leitch also said that the natural evolution of some cancers is rapid, of others is slow, and the rate of growth and the type of metastases are often unpredictable. All of us have made the same observation as surgeons and radiologists—the surgeon on the one hand, feeling confident that he has removed all of the disease only to have the patient return with a recurrence, the radiologist on the other hand with the radioresistant tumor that requires surgical removal. There should be no fight between the advocates of radium and surgery over the best treatment for cervical cancer. Both modalities will cure about the same percentage of patients, namely, 55 per cent. Moreover, when surgery fails, radiation takes over; when radiation fails, surgery takes over and that is the way it will be for a long time to come.

Leitch's advanced cases reflected a time interval of only 3 months from the first symptom to the time of death in the shortest instance and up to 7 years in the longest instance, for an average of 1 year and 9 months. Today more and more early cervical cancer cases are being discovered as Stage 0 or carcinoma in situ. These early cancers are often asymptomatic and have been known to remain dormant for long periods of time. Early diagnosis will do as much as or more than improvements in surgical and radiation techniques to reverse the course of cervical cancer from one of gloom and doom to one of hope and cure.

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The surgical treatment of cancer of the cervix

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THE factor of surgical mortality was the principal deterrent to surgical attack upon cancer of the cervix during the early years of this century. With the advent of radiation therapy, which seemed to have a low immediate mortality, and with the realization that cancer of the cervix was a radiosensitive lesion, sentiment rapidly swung to radiation as the principal method of treatment. However, in certain quarters, namely Austria, and in certain Gynecological Services, namely Bonney in London and Jean-Louis Faure in Paris, primary surgical attack was never abandoned in the face of general adoption of radiation therapy.

With surgical procedures rendered much safer for the patient and with the eventual realization that radiation was not the panacea for cancer that at first with optimism was expected of it, interest has again been focused on the surgical attack. Meigs of Boston must be credited with sparking a revival of surgical interest on any appreciable scale in the United States. His earlier cases were highly selected but this was of necessity, in view of the widespread acceptance of radiation as the treatment of choice in this country. The question now, as always, is which is the more effective primary treatment, surgery or radiation.

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Case material

This report will deal with a series of patients operated upon 5 or more years ago in the course of a planned complete surgical program begun in Memorial Hospital in September, 1947. The patients were operated upon with minimal selection. As stated in previous reports, age, obesity, and concomitant medical complications did not serve to contraindicate operation except in extreme instances.

The operation envisaged was a radical hysterectomy with pelvic node excision. The latter consists of a complete excision of pelvic nodes together with fatty tissues of the retroperitoneal pelvic spaces. The technique has been previously described.[1] The only structures remaining are the bladder, lower half of vagina, pelvic colon, obturator nerves, ureters, and external iliac vessels. The hypogastric vessels and adherent nodes and tissues are excised with denudation of the sciatic nerve roots. The patients, both private and service patients seen in the clinic and/or admitted to the hospital, are described in Table I. If the private patients of staff members were admitted to the hospital they are included in the series. Private patients seen in staff members' private outside offices only and possibly treated in other hospitals are not included.

In clinical practice it is not possible to develop a "pure" surgical series because with the widespread use of radiation many patients had received preoperative radiation elsewhere. If this radiation was given within 6 months prior to operation the patient was

Table I. Summary of patients

Operated upon to "cure"	523
Exploratory laparotomy only because of nonresectable disease	10
Palliative operation—only possibility	19
Primary radiation*	83
Refused treatment	42
No treatment offered	6
Consultation only	4
Recurrent carcinoma of the cervix	493
Radiation necrosis only	42
Radiation complications (no recurrence of cancer found)	20
Successfully treated elsewhere (follow-up only)	22
Total	1,264

*The reason for radiation: referred from outside source to radiation therapy department, 6; private patients of staff member early in surgical era, 13; refused operation, 13; widespread metastases, 17; very poor medical risk, 30; had primary cancer elsewhere, 3; reason not determined, 1; total, 83.

Table II. Five-year survival

Stage	*No preoperative radiation*	*Preoperative radiation**
I	125/164 (76.2%)	32/38 (84%)
II	84/163 (52%)	27/51 (53%)
III	10/37 (27%)	2/10 (20%)
IV	6/40 (15%)	3/11 (27%)
Not classified	0/5 (0%)	3/4 (75%)
Total	225/409 (55%)	67/114 (59%)

*The preoperatively radiated group includes 24 patients whose specimens were reported as showing no residual cancer. Twenty-two of these lived 5 years and 2 died later of metastases. If these are excluded, the salvage rate for the preoperatively radiated group would be 50 per cent.

empirically classified as one who had received preoperative radiation. Moreover, a limited number, private patients of one staff member, received preoperative radiation by means of local application of radium because of this doctor's conviction that this was a procedure beneficial to the patient. These patients admitted to Memorial Hospital could not be disregarded and are included in the preoperatively radiated group.

Five-year results

The results in patients operated upon to "cure" and not previously treated are summarized in Table II. In Table III the patients are classified according to the surgical and pathological classification.[2]

The differences in the results between preoperatively radiated patients and those not receiving radiation are considered insignificant. It continues to be the policy of the service *not* to give preoperative radiation.

Modes of surgical therapy

In consistently attacking cancer of the cervix surgically it is not sound surgical judgment to attempt a standard procedure in every instance. Consideration must be given to the status of the patient and the apparent extent of the disease encountered. Therefore, a variety of procedures is avail-

Table III. Results of surgical treatment of cancer of the cervix

Surgical and pathological classification	*No preoperative radiation*			*Preoperative radiation*		
	No.	*Living 5 years*	*%*	*No.*	*Living 5 years*	*%*
A	123	98	80	24	21	87.5
B	116	73	63	15	8	54.4
C	31	18	58	10	3	33.3
CN	12	4	33.3	4	2	50
D	34	15	44.1	14	7	50
DC	29	8	27.5	10	1	10
E	31	4	12.9	5	2	40
EN	21	3	14.3	1	0	0
F	3	1	33.3	1	1	100
FN	9	1	11.1	6	0	0
PRAO	—	—	—	24	22	91.7
Total	409	225	55	114	67	58

Key to abbreviations:

A, limited to cervix; B, extends to corpus or vagina; C, parametria involved; CN, as C with parametrial nodes positive; D, positive nodes, periphery of pelvis; DC, same with parametrial invasion; E, bladder and/or rectum involvement; EN, same with positive peripheral nodes; F, bladder and/or rectum involvement, pelvic floor involvement, distant metastases; FN, same with positive nodes; PRAO, biopsy positive, preoperative radiation, negative specimen.

able and the surgeon should adopt the one which in his judgment is the most appropriate. In the series dealt with here the various procedures that were employed are summarized in Table IV, with indications of 5-year survival incidence and surgical mortality. Excluding the pelvic exenteration operations, the mortality was 0.7 per cent. The mortality for 76 patients with anterior, posterior, and total exenteration was 9 patients or 11 per cent.

In 15 instances a total hysterectomy was performed with 13 five-year survivors. Total hysterectomy is admittedly inadequate treatment for cancer of the cervix but was carried out in these highly selected patients because the lesions were small and the patients either were very obese or had been judged poor risks for more extended procedures.

It goes without saying that in a series of patients reported as having had surgical treatment for cancer of the cervix, with essentially one type of operation only, there was a degree of selection exercised, consciously or unconsciously, because one operation alone cannot meet the situations in *all* cases that may be presented for treatment.

Lymph node involvement

Because a surgical specimen, often with pelvic nodes, was obtained, it was possible to estimate the incidence of lymph node metastases. The findings with results of treatment are summarized in Table V, and the international clinical diagnosis is correlated with lymph node metastases as found in the surgical specimen.

Here again, the factor of radiation therapy enters the picture in this series. In one single instance early in the series there was recurrence in the left parametrium following a Schauta radical vaginal hysterectomy 3 years previously. This recurrence was confirmed at laparotomy and by biopsy. Following 4,000 r, 1 Mev radiation to the pelvis, the patient has remained well for 9 years. This is the only instance of postoperative recurrence controlled by radiation in the series. When positive nodes in the pelvis are excised it is nevertheless hardly justifiable in the patient's interest not to essay any and all measures to control the disease. Hence, on the theory that in some instances, at least, highly radiosensitive cervical cancer may have been present, postoperative "prophylactic" radiation therapy was given in a number of instances where positive nodes were present. This radiation was given at 1 Mev to deep pelvic dose of 2,000 to 4,000 r through a large anterior and posterior port. Sometimes it consisted of about 2,000 r deep pelvic dose given through 4 to 6 pelvic ports with a 250 kv machine.

Omitting detailed discussion, a review of the series of patients with positive pelvic nodes who received preoperative and/or postoperative prophylactic radiation and those who did not shows there is no unequivocal evidence to substantiate the value of the radiation (except in the single instance described).

Postoperative fistulas

The incidence of ureterovaginal fistulas among 447 patients operated upon and excluding exenteration procedures was 39 or 9 per cent. The incidence of vesicovaginal fistulas was 30 or 7 per cent. The combined total was 16 per cent. The fistulas were managed by a variety of methods. Seventeen

Table IV. Type of operation and 5 year survival—all stages

Operation	*5 year survival*	*Surgical mortality*
Total hysterectomy	13/15 (87%)	0
Classical Wertheim	8/20 (40%)	1
Schauta radical vaginal hysterectomy	24/34 (71%)	1
Radical hysterectomy (Wertheim) pelvic nodes	209/340 (61.4%)	1
Excision stumps, pelvic nodes	20/36 (56%)	0
Anterior pelvic exenteration	11/40 (28%)	3
Total pelvic exenteration	4/33 (12%)	5
Posterior pelvic exenteration	1/3 (33%)	1
Excision stump	2/2	0
Total	292/523 (56%)	12 (2.3%)

Table V. Five-year results related to presence or absence of pelvic lymph nodes

Stages	*No metastases*	*Incidence of node metastases*	*Pelvic node metastases*
I	143/175 (82%)	13%	13/27 (52%)
II	90/150 (60%)	30%	20/64 (31%)
III	10/26 (38%)	46%	2/21 (10%)
IV	5/24 (21%)	53%	4/27 (15%)
Not classified	3/8 (37%)		0/1 (0%)
Total	251/383 (66%)		40/140 (29%)

of 30 vesicovaginal fistulas closed spontaneously on catheter drainage. Seventeen of 32 unilateral ureterovaginal fistulas closed spontaneously. The incidence of spontaneous closure of all fistulas was 34 of a total of 62 fistulas, i.e., 55 per cent (excluding 7 bilateral ureterovaginal fistulas). Included in the total number of fistulas are 7 instances of bilateral ureterovaginal fistulas. Thirty-eight of the total of 69 patients that developed fistulas lived 5 years free from cancer, i.e., 55 per cent.

Comment

It has become apparent that the question of surgery or radiation as the principal treatment of cancer of the cervix cannot be decided by comparing one series of patients treated by one method with another series treated by the other method in another institution. Even parallel series in the same institution cannot be rigidly compared. It is our opinion that in the present stage of knowledge both radiation and surgery are effective forms of local treatment but it would seem preferable to excise a cancerous organ together with adjacent lymph nodes rather than treat the cancer in situ, provided that the risks of mortality and morbidity are not inordinately great incident to the required operation.

If more and more gynecologists and surgeons are to engage in a surgical attack upon this disease, such programs can hardly be fully initiated at first. The requisite operations are complex, the complications have to be anticipated and managed. It is in order, therefore, that, in the initiation of surgical programs, those to be engaged therein have the proper surgical backgrounds and technical proficiencies and the knowledge to meet the various complications as they arise. In the initiation of such programs only the smaller lesions in good risk patients should be operated upon and, as proficiency and experience increase, the more extensive lesions may be attacked.

Conclusions

Modern surgery is an effective method for the treatment of cancer of the cervix.

In a series of 523 minimally selected patients the over-all 5-year salvage rate was 56 per cent for patients with clinical Stage I, II, III, and IV lesions.

The surgical mortality was 0.7 per cent for all operations except exenterations. The surgical mortality was 11 per cent for patients receiving partial or total pelvic exenteration. The over-all surgical mortality was 2.3 per cent.

Surgical mortality and morbidity are no longer effective arguments against the surgical treatment of cancer of the cervix.

Both radiation and surgery are forms of local therapy. From an objective and perhaps empirical point of view it would seem, to us at least, that in the present state of knowledge definitive excision of a cancerous organ is the preferred treatment for cancer in that organ when the incidence of mortality and morbidity is not prohibitive.

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Surgical experience in cancer of the cervix

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THIS is a preliminary report on a series of cases of squamous cell carcinoma of the cervix, treated at Walter Reed General Hospital over a 15 year period. Three contrasting series of 5 years each, using a different mode of treatment during each period, were established.

Comparison of the results of 3 modes of treatment—surgery alone, irradiation alone, and a combination of surgery and radiation—is herein presented.

Modes of treatment

In the first 5 years the surgical approach to the problem was emphasized primarily to correlate findings with the reports of others.[2-9] During this period (Table I), 76 per cent of the patients were treated by primary operations, 12 per cent by a combination of radiation and then operation, while 12 per cent were treated by radiation only. The latter group represented patients on whom exploratory operations were performed and who were found to have disease outside of the pelvis, or those found to have medical contraindications to a surgical procedure.

In the second 5 years, with the experience gained by the Radiation Therapy Department with million-volt therapy during World War II, a combined approach was used employing radium and external radiation, followed by surgery. Eighteen per cent had primary operations, 70 per cent had primary radiation (mostly combined radium and million-volt therapy) followed by definitive surgery, whereas again 12 per cent had radiation only as in the first 5 year group.

In the third 5 year program individualized therapy, pending results of the first two programs, was instituted. In this group, of which 4 years have been completed, again 18 per cent had primary operations, 78 per cent had preliminary radiation (mostly radium alone in Stage I and Stage IIa) followed by definitive surgery, and 4 per cent had radiation only.

Material

From November, 1945, to January, 1960, 963 patients were referred to Walter Reed

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Dr. Carlton Price, Chief, Gynecology Service, Dr. Milton Friedman, Chief, Radiology, and Dr. Wm. E. Randall, Pathology Service, were the principal participants when this series was initiated in November, 1945.

A report by Drs. Laman A. Gray, Milton Friedman, and Wm. S. Randall on a small group of women having adenocarcinoma endometrium who were found at operation to have residual carcinoma after massive preoperative radium therapy inspired the present study.

Presented at the first meeting of the New York Gynecological Society, New York, New York, Sept. 16, 1960.

General Hospital for treatment of preinvasive and invasive carcinoma of the cervix. These patients were referred from outlying station hospitals of the Armed Forces in the eastern half of the United States, overseas stations throughout the world, and civilian hospitals caring for eligible dependents. Fifteen per cent (140) referred for carcinoma were found not to have the disease after cytological smears, biopsy material, and rebiopsy material failed to substantiate the transfer diagnosis, and, therefore, these patients were not treated as oncology cases. Fifteen per cent of the patients transferred with a diagnosis of invasive disease proved to have in situ lesions after study, and were treated accordingly. Much of this pathological material has been reviewed by the Armed Forces Institute of Pathology for the Walter Reed Pathology Service.

Concurrent with cytological and pathological study, each case was clinically staged according to the League of Nations classification by the Gynecology and Radiation Therapy Services (as a team) and graphically recorded on the 3 dimensional anatomical diagrams prior to therapy.* The pretreatment history, physical examination, x-ray examinations, and laboratory survey were recorded on a history and treatment IBM form. The detailed gynecological history included such items as age at marriage, number of marriages, age at first coitus, frequency of coitus, circumcision of husband, history of leukorrhea, douching habits, family history of carcinoma, interval between onset of symptoms and therapy, etc. Cytological studies were continued during therapy, after completion of therapy, and during subsequent follow-up examinations.

Annual oncology follow-up studies were conducted through a special outpatient clinic. This follow-up consisted of chest x-ray examinations, excretory urogram, barium enema, skeletal survey, and blood study (with emphasis on total protein, A-G ratio, alkaline phosphatase, prothrombin time, bilirubin and urea nitrogen), circulating cell study, and other special tests as indicated. As the result of excellent liaison between patients and physicians, a follow-up rate of 94 per cent has been accomplished to date.

*League of Nations Manual.

Incidence of disease according to stage

Of the 823 patients treated, 595 patients were treated between 1945 and December, 1957, and have a follow-up of 2½ years or more. In our study there is a rather close prognostic correlation between the 2½ and the 5 year survival figure. Two hundred and twenty-eight patients treated since January, 1958, are not included in the survival figures (Table II).

A breakdown of cases into stages for the 13 year period revealed that 23.86 per cent, or 142 patients, had carcinoma in situ, or Stage 0. Stage I comprised 43 per cent; Stage II, 17.1 per cent; Stage III, 7.56 per cent, and Stage IV, 8.4 per cent. In comparing this distribution with that during the 1958 to 1960 period, we found very little difference; a drop of 2 per cent of Stage IV and 5 per cent of Stage II, and an increase of 9 per cent in Stage I. This does not appear to be a significant shift. However, if we divide our cases according to stages into three 5 year periods, then we see a significant change. Stage 0 cases doubled at the expense of Stage I, which dropped from 57 per cent to 44 per cent.

In clinical staging our surgical experience revealed that pelvic inflammatory disease, endometriosis, and/or postoperative pelvic adhesions can be responsible for overstaging in some instances. Laparotomy, either primary, exploratory, or following radiation, is of great value in assessing the true extension

Table I. Form of therapy in three 5 year series

Therapy	*1945-1950 (%)*	*1951-1956 (%)*	*1956-1960 (%)*
Radiation	12	12	4
Radiation and surgery	12	70	78
Primary surgery	76	18	18

Table II. Classification of cases as to clinical stage

Stage	1946-1957		1958-1960		Total
	No.	%	No.	%	
0	142	23.86	50	21.93	192
I	256	43.08	118	51.75	374
II	102	17.14	28	12.28	130
III	45	7.56	17	7.45	62
IV	50	8.40	15	6.58	65
Total	595	100	228	100	823

of the disease; and herein surgery plays a distinct role.

A critical analysis of staging disease has been obtained in those patients who had surgical procedures after the diagnosis and treatment of their disease. In Table III we see the error in our clinical staging. With the exception of 21 per cent of Stage III, our error was in the understaging category. The overstaging of clinical III is caused mainly by the presence of chronic pelvic inflammatory disease, endometriosis, and adhesions. In this study the clinical stage is never changed, but a postradiation and surgical (pathological) stage of disease is recorded.

Age distribution

Age distribution ranged from 19 to 83 years in this series. It is observed that the median age for Stage 0 is 36 years, and for invasive carcinoma, 43 years. This may be indirect evidence that it takes several years for in situ disease to become invasive. The median age difference in the invasive clinical stages is not significant. Our patients as a group are younger than those reported in other clinics, because of the fact that in the military service we care for a group of patients with a larger percentage of younger people.

Pregnancy and cervical carcinoma

The incidence of pregnancy complicating carcinoma of the cervix in our series is 3 per cent. Therefore, we feel that cervical cytological examination is indicated routinely at the time of the first prenatal visit, any time during pregnancy when leukorrhea or bleeding is noted, and again at the postpartum visit. Screening of obstetrical and gynecological patients has been enhanced by the adoption of fluorescence microscopy with acridine orange.[10]

Surgical technique

The surgical technique for carcinoma in situ is discussed in another paper.[11] The technique employed for radical hysterectomy with lymphadenectomy in the primary surgical group has in general been similar to Meigs' technique. However, following the decision to discontinue the combination of radical radiation and radical hysterectomy with lymphadenectomy in the second 5 year period, a technique was evolved for Stage I and IIa cases. This consisted of a Cherney incision, extraperitoneal lymphadenectomy of secondary nodes, as per the urological approach,[12] starting at or above the inferior mesenteric artery, and continuing down the primary nodal chain. This included all presacral nodes, plus stripping of the sheath of all vessels from the inferior mesenteric artery to obturator foramen, the femoral canal, and to the origin of the obliterated hypogastric. The Stage I and IIa cases showing good radium response clinically and by cytological examination had a modified Wertheim procedure, which included tissue to the limits of Point A (the site of the uterine artery crossing the ureter). All others had radical hysterectomy. All Stage IIb, III, and IV patients had preliminary radium and external radiation followed by exploration (through a vertical abdominal and transperitoneal approach) in 4 to 8 weeks. If disease was localized to the pelvis, radical lymphadenectomy and radical hysterectomy were performed.

Table III. Error in clinical staging

Stage	Understaging (%)	Overstaging (%)
I	21.1	0
II	33.3	0
III	26.0	21
IV	2.0	0

If surgery was used primarily and radiation then prescribed, it was for palliation following the surgical exploration in which metastatic disease was found. If radiation was primarily used and an operation was indicated, it meant that a radioresistant lesion was present and exploration followed.

Obesity

One of the classical entities precluding the use of surgical intervention prior to or following radiation was the problem of obesity. In this study, 10.4 per cent of patients were obese. The over-all incidence of major and minor surgical complications, excluding sepsis, was 28.1 per cent with obesity, and 23 per cent without obesity. The incidence of major surgical complications, exclusive of sepsis, was 12.5 per cent with obesity and 13.9 per cent without obesity. The incidence of complications, therefore, was not much different. However, the incidence of sepsis following operations was 53.1 per cent with obesity and 21.2 per cent without. Herein lies the main hazard in treating the obese patient surgically.

Pathology of the uterus

In the over-all survival assessment, 46 per cent of the lesions were of the endophytic type, and 49.4 per cent were exophytic, with the remainder unclassified. In Stage I lesions, 25 per cent of the cervices had residual carcinoma in spite of cancerocidal dosage of radium and/or radiation. Of interest was the fact that the 5 year survival of patients with Stage I lesions with residual carcinoma in the cervix but without nodal involvement was 80 per cent, whereas in those with neither residual carcinoma in the cervix nor nodal involvement it was 93.5 per cent.

Cervical stump carcinoma in this series was 6.2 per cent. It was for this reason that prophylactic trachelectomy[13] for the retained stump was initiated in our clinic in 1952.

Lymph node involvement

To date, we have not found any positive nodes in cases of carcinoma in situ or in cases of superficial stromal invasion or microinvasion. In Stage I lesions treated with primary operations the incidence of positive nodes is 16 per cent. In this study an over-all rate of 19 per cent was obtained for Stage I lesions (40 cases), 35 per cent (20 cases) for Stage II, 64.3 per cent (14 cases) for Stage III, and 57 per cent (4 cases) for Stage IV (Table IV). The 5 year survival rate was 45 per cent for Stage I, 25 per cent for Stage II, 42.8 per cent for Stage III, 0 per cent for Stage IV. Of 9 patients who underwent exenteration and who were followed over 5 years, 3 of 8 patients with positive nodes survived 5 years.

Table IV. Survival rate in patients with nodal involvement according to stage (1945 to 1957)

Stage	*Positive node cases*	*No. alive*	*% survival*
I	40	18	45
II	20	5	25
III	14	6	42.8
IV	4	0	0

In the study period of 1951 to 1955, there were 86 Stage I patients who had preliminary radium and/or radiation followed by operation. Fifty-six of these patients had preliminary radium with a cancerocidal dose to Point A. Fourteen of these had positive primary lymph node involvement (25 per cent). Of 30 patients who had radium therapy followed by million-volt therapy and then operations, 6 had positive nodes, or 20 per cent, which is approximately the same nodal incidence as in Stage I with primary operations.

Most of these cases were reviewed by the Armed Forces Institute of Pathology. In Stage I disease, lymphadenectomy averaged 50 to 60 nodes for study. In several cases a study involving sectioning a positive node, marking it with a silver clip, giving it full cancerocidal million-volt therapy, and then reoperating in 4 to 6 weeks revealed viable tumor still remaining in the node. On this basis, it was felt that one could not assume

Table V. Survival rate—Meigs-Brunschwig surgical classification (1945-1957)

Class	*% survival*	*No. of patients*
O	100	142
A_0	84.3	106
A	81.6	112
B	52	19
C	35.7	12
D	32.9	46
E	27.2	8
F	11.1	8
Total		453

that in any individual case radiation was effective in destroying carcinoma in nodes. Surgery was a positive approach to this study problem, rather than an exercise and was effective therapy in 25 to 35 per cent of positive node cases. Survival in this group with primary nodes irrespective of the stage was 37 per cent, and with secondary nodal involvement it was 12.1 per cent. A breakdown on survival according to the numbers of nodes involved will be part of a subsequent report.

Fistula formation

In the first 5 year period of this study, the ureterovaginal and vesicovaginal fistula rate from therapy was 16.3 per cent related to the 76 per cent in which the primary radical hysterectomy and lymphadenectomy approach was used. The rectovaginal fistula rate for this period was 9.1 per cent.

In the second 5 year period 70 per cent of the patients had preliminary radium and million-volt therapy followed by radical operation during the first 3 years of this period. This had to be modified in the last 2 years of the period to preliminary radium followed by radical operation because of multiple complications, difficulty of dissection, etc. The fistula rate for this period was reduced to 9.7 per cent ureterovaginal and vesicovaginal fistulas by not stripping the ureters from the peritoneum, by not tying off the obliterated hypogastric arteries, and by resorting to extraperitoneal suction drainage. The rectovaginal fistula rate was 7.8 per cent.

In the third 5 year period further reduction of ureterovaginal and rectovaginal fistula rates to 6.5 and 5.0 per cent (through 1958) was probably related to selective radium application plus selective operations. In Stage I and IIa cases the preliminary radium was followed in 4 to 8 weeks with selective operations including extraperitoneal lymphadenectomy.

As a result of survival and complication figures in the third 5 year series to date, continued investigation using this combined approach is in order.

Survival by Meigs-Brunschwig surgical classification

Cases in which the surgical specimen was available for study are included in this statistical classification. As expected, a typical progressive loss in survival rate of 311 patients with invasive carcinoma of the cervix classified according to the Meigs-Brunschwig method was noted in this series. Our study showed that Classes A, A_0, and B can also have primary and/or secondary nodal involvement determined best today by surgical exploration. Of the Class A patients treated by primary operations, the survival rate was 89.3 per cent, and with radium followed by operation, 82.7 per cent (Table V).

Survival as to stage and modality of treatment (1945 to 1957)

In Stage I (Table VI) there were 65 patients treated by primary operations with a survival rate of 84.4 per cent; 65 patients treated with preliminary radium followed by operation with a survival rate of 83.9 per cent; 40 patients treated with radium and operation followed by external radiation with a 64.1 per cent survival; 30 patients treated with radium, external radiation, followed by operation with 46.6 per cent survival; and 11 patients treated by operation followed by radiation with a 9 per cent survival. In 9 of the latter group the disease was clinically understaged at the time of the surgical procedure and the only survivor was a patient with a surgical Stage I lesion with lymphatic permeation of cervical

stromal lymphatics and a highly anaplastic lesion, for which postoperative radiation was advised.

In Stage II the survival of 75 per cent of a group of 19 patients with the use of radium, then operation, will require greater consideration in the future as the modality of choice, particularly in Stage IIa lesions. Stage III and IV lesions are treated primarily with radiation in this series, but surgical exploration is warranted thereafter for complete evaluation.

Table VI. Survival as to stage and modality of treatment

Treatment	Stage I		Stage II		Stage III		Stage IV	
	No.	%	No.	%	No.	%	No.	%
Radiation only	34	59.3	28	21.4	19	16.6	23	0
Operation only	65	84.4	6	57.1				
Radium and operation	65	83.9	19	75	5	20		
Radium, operation, external radiation	40	64.1	14	30.9	4	25	2	0
Radium, external radiation, operation	30	46.6	28	58.8	7	25	1	0
Operation, radiation	11	9	4	25	2	0	1	100

Table VII. Survival related to patient delay in diagnosis

Time (months)	Stage I (%)	Stage II		Stage III		Stage IV	
		No.	(%)	No.	(%)	No.	(%)
1	84.3		63.3	10	10	6	0
2	80		26.6	3	33	2	0
3	51	6	33	4	33	3	0
4	63.6	6	33	1	0	1	0
5	60	4	50				
6	44.2	6	66	4	25	5	0
Over 6	38.9		23	4	0	6	0

Table VIII. Survival related to physician delay in treatment

Time (weeks)	Stage I (%)	Stage II (%)	Stage III		Stage IV	
			No.	%	No.	%
1	84.1	75	7	0	6	0
2	77.5	20.9	3	0	4	0
3	57.1	21	4	25	1	0
4	54	40	4	75	2	0
Over 4	66	20	10	10	9	0

Table IX. Distant metastases as related to treatment and stage

Procedure	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)
Radiation only	7.1	35	22.2	35
Operation only	7.0	37.5		
Operation followed by radiation	30	50 (4 cases)		
Radiation followed by operation	17.2	20.4	30.8	

Over-all survival

The over-all survival figures of 72.3 per cent (including Stage 0) and 63.3 per cent (excluding Stage 0) attest the necessity for early diagnosis and early treatment. The survival figures for this study are dependent on clinical staging since approximately 15 per cent of the cases fall into the Stage III and IV grouping. It is the ultimate goal of detection clinics to get patients into the early categories. Suffice it to say that approximately 15 to 20 per cent of patients with Stage I lesions have vascular and/or lymphatic spread, and these are the patients who confound the therapist. Pending possible chemotherapeutic or immunological means of controlling this disease, it is apparent that the time interval (local growth) and patient resistance (lymphatic and hematological spread) will be determining factors in the progression of this disease. Obviously, if tumor excision is complete one cannot expect recurrence in tissue that was successfully removed. However, this is not true in tissues treated by radiation but left in situ. There is the possibility of later recurrence locally or with lymphatic or vascular spread from a retained but smoldering nidus.

Survival related to delay in diagnosis or patient delay. Again, there are too few cases in Stages III and IV to be of statistical significance, but with Stage I and II lesions it is apparent in Table VII that survival of a patient is directly related to the procrastination of reporting of symptoms.

Surgical mortality as to stage. Any postoperative death within 30 days following a surgical procedure was considered a surgical death. In the group of cases from November, 1945, to January, 1958, there were 2 such deaths in Stage I, or 0.8 per cent, and 1 in Stage III, or 2.5 per cent. No surgical death occurred in Stage 0, Stage II, or Stage IV. The majority of the latter operations, however, were explorations only or emergency gastrointestinal or genitourinary diverting procedures. This low rate justifies continued investigation of the surgical role in this problem.

Hospital mortality as to stage. Hospital mortality included any patient having an operation and/or radiation, but who died after the thirtieth day of the initial hospitalization. This was none for Stage 0 and Stage I, 1 case in Stage II, or 0.9 per cent, 2 cases in Stage III, or 5 per cent, and 6 cases in Stage IV, or 12 per cent.

Survival related to physician delay in treatment. Table VIII indicates in time intervals the survival rate according to the stage of the disease as related to physician delay. There are too few cases in Stages III and IV to be of statistical importance, but in Stages I and II delay of therapy is directly proportional to survival. It seems logical in a preliminary report of a study to assess each entity in proper light. Time is an important element not only in a patient's report of abnormal signs and symptoms and a physician's delay, but in therapy interval as well. Time lost with radiation therapy (especially in radioresistant disease) may be a factor in the survival rate. We need a means of recognizing such cases. We are employing the fluorescent cytology technique to elicit such clues by study of circulating cells, buccal mucosa, cytological changes during radium, and/or radiation therapy. It is too early in this study to report the efficiency of this approach.

Distant metastases (embolism) as to treatment and stage. There were staged lesions in which laboratory or roentgen tests proved the existence of a metastatic lesion or autopsy subsequently proved its presence. As noted in Table IX, there appeared to be no difference in the incidence of distant metastases in Stage I or Stage II disease in which radiation alone or surgery alone was the modality of choice.

Comment

In this preliminary report on a 15 year study of cancer of the cervix at Walter Reed General Hospital, we are presenting an evaluation of the experience with surgery as primary treatment, an evaluation of the accuracy of clinical staging, a determination of the incidence of nodal involvement, an assessment of the effectiveness of radia-

tion therapy, and an evaluation of the role of combined radiation and surgery as adequate therapy with a reduced complication rate. Studies of this type can best be accomplished in centers equipped to treat all stages of disease and complications and to follow such cases. Cytological screening will assist materially in eliciting malignant lesions in the earlier stages of the disease.

Summary

1. Clinical staging is necessary, but is an inaccurate method for categorizing disease.

2. Surgical and/or pathological staging is effective in estimating extent of disease and prognosis thereof.

3. Surgical treatment is a positive approach to nodal involvement, residual disease in the uterus and vagina, and to radioresistant disease.

4. The lowered fistula rate, the lowered surgical complication rate, and the low surgical and hospital mortality rates permit more consideration of the role of surgery in treatment.

5. Combined therapy in cancer of the cervix warrants further consideration.

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Discussion

Dr. Langdon Parsons, Boston, Massachusetts. For some time I have been interested in the surgical treatment of cancer of the cervix. I am deeply grateful to Dr. Brunschwig and Dr. Riva for reporting on nearly 1,000 surgically treated patients. Perhaps now some of our arguments in favor of operation will carry more authority. There is general agreement that the majority of patients with unsuccessfully treated cervical cancer die within the first 36 months and usually within the first 2 years. The drop in the number of survivors between 5 and 10 years is less than 5 per cent. Recurrence after 10 years is practically unknown. Cancer of the cervix, unlike other forms of malignant disease, is not only preventable but also curable in a very high percentage of cases.

In the past few years Dr. Friedell and I have carried on a study of surgical specimens, which have been blocked in paraffin and then sectioned serially, thus giving us an opportunity to look at the whole specimen. We have come to the conclusion that cancer of the cervix is basically a local disease spreading in tissue spaces perhaps as often in a fore and aft direction as it does laterally. The spread tends to follow the distribution of the parasympathetic nerves. The nodes are involved in 15 per cent of Stage I cases and 25 per cent of Stage II cases, but far less often than is generally believed.

The 5 year cures reported here are excellent because the operation performed was extensive enough to encompass the total amount of disease present. This means that a very extensive dissection was done around the base of the bladder and the vaginal wall as this is the area of distribution of the parasympathetic nerves.

One should, of course, dissect the nodes, for 50 per cent of Stage I and 2 per cent of Stage II cases with positive nodes will be salvaged. You will not, however, obtain a 5 year result if you do a good node dissection but fail to do an adequate dissection in the area in and

around the primary tumor. The radical operation should stress the local dissection, not the nodal excision.

For further indication of the local nature of cervical cancer, one may point to the fact that even after radiation failure it is still possible to cure cervical cancer. In a series of 100 operations for recurrence after radiation failure a 35 per cent 5 year salvage was obtained in the group where the recurrence was local and no distant metastases were present.

In approximately 30 per cent it was still possible to perform a Wertheim hysterectomy with node dissection. The salvage rate in this group was 65 per cent, rising to 85 per cent when the nodes were negative. A 21 per cent salvage was obtained when the patient had enough disease to require exenteration.

I have always been interested in (1) how cancer got to the nodes, and (2) what part blood vessel invasion played in the life history of cancer of the cervix. We have assumed that the nodes became involved by penetration of cancer cells along lymphatic channels. While I believe that cancer does reach the lymph nodes through lymphatic channels, I have yet to confirm it either in cancer of the cervix or in breast carcinoma. On the other hand, we do see nests of cells in small blood vessels in the periphery of the nodes and have traced it into nodes.

The spread of cancer of the cervix by blood vessel invasion has not been emphasized for the simple reason that the specimens have never been subjected to adequate study. Although you may see occasional tumor emboli when the pathological material is stained with hematoxylin and eosin, it really takes special elastic tissue stains to bring out the true picture.

On the basis of an incomplete study of 90 cases we have found that when tumor was seen in blood vessels 2 of 3 patients died in contrast to 2 of 3 surviving when no blood vessel invasion was noted. The fact that the blood vessels may be involved could explain, in part, why some patients with seemingly adequate surgical excision developed recurrences and died.

Dr. Joshua William Davies, New York, New York. For several years there has been a definite need in New York for a Gynecological Society which was not a club, but an organization to which every physician showing a serious interest in gynecology and its correlated ramifications is eligible for membership. You 80 outstanding colleagues, by your presence at this first meeting, attest your sympathy for such a society.

It shall be the purpose of the New York Gynecological Society to invite distinguished speakers who welcome your comment and encourage further correspondence with them. It is desired that each member concentrate on some particular subject, feel free to discuss it with fellow members at the social hour and later present it to the society as a formal presentation, a case report, or a scientific exhibit. This society, being incorporated, shall be a repository for donations to research which shall be distributed by the Directors to those institutions whose members apply for assistance in research or educational purposes.

This evening we have been favored by an exceptional presentation on the "Surgical Treatment of Carcinoma of the Cervix." It barely seems possible that I have been interested in this subject for over 37 years. During this time most patients at the Woman's Hospital were treated with the application of radium followed by roentgen rays; other patients were treated first with roentgen rays and later radium was applied. The patients so treated were followed in the clinic at monthly intervals for a year; during the second year they were followed at bimonthly intervals; and some were seen at intervals of 3 months during the third year. Complications due to concurrent radiation of the adjacent structures were at times as difficult as the disease itself.

So dominant were gastrointestinal symptoms of burning, diarrhea, bleeding, and spasm that it became advisable to establish a special clinic for the relief of these complaints. The surgically treated patients with carcinoma of the cervix, so treated because of other pelvic disease, presented an entirely different convalescence. They were not anxious, apprehensive, uncomfortable, or unable to return to work; they appeared optimistic and desired re-employment.

Despite the relative comfort of the surgically treated patient, lack of imagination and fear or obstetrical fatigue prevented the institution of a surgical program in a hospital revered for its surgical contributions. During the years 1950 through 1956, there were 208 patients treated for carcinoma of the cervix: all were treated with radium and x-ray, except 50 patients. Of these 50, 6 underwent radical hysterectomies. The other 44 were patients in whom the carcinoma

was discovered after the uterus was removed for other reasons and, therefore, the treatment was less radical.

You may be pleased to know that our present Surgical Director, Dr. Carl Javert, has supported a program of selective therapy, which includes surgical treatment, at the Woman's Hospital. During the last 3 years, there have been 120 patients treated for carcinoma of the cervix. 50 of these have been treated by planned operation. Although this is still less than half of the total number, it is double the number treated by operation in the previous 6 years, and eight times the number of planned operations. It is too soon to be able to evaluate our results with any significant statistics. We sincerely hope that this trend toward surgery will continue and that those members of the staff who are interested and equipped for this rather enervating therapy, which facilitates the patients' convalescence; will be instructed and encouraged in their dedicated work.

Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix

A 5 year follow-up

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MODERN methods of radiotherapy for carcinoma of the cervix have yielded results which, for large unselected series of patients, have not been matched by any other mode of treatment. Increased dosage levels, responsible in part for improved cure rates, have not infrequently been accompanied by larger numbers of radiation injuries.[1, 2] A plan to correlate radiation dosage and injury rate was placed in effect at the Radiumhemmet in 1953. A preliminary report on this study was presented in 1957.[3] All patients in this series have now been followed for more than 5 years and these results have been analyzed.

The principles of treatment under the current Stockholm method, individualization and intensive, divided courses of therapy, are well known and have been presented elsewhere.[4, 5] It should be noted that the period with which this study is concerned was one of experimentation during which many patients, especially those with advanced lesions, were treated with extremely large and intense intrauterine doses of radium. It is to be expected, therefore, that the injury rates found in this group of patients will be higher than those encountered either before or after this period. The relatively high incidence of injury makes statistical analysis of these data more profitable than it would otherwise be.

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Material

The cases studied were those of 500 consecutive patients with invasive carcinoma of the cervix treated at the Radiumhemmet in Stockholm from July, 1953, through August, 1954. The distribution was:

Stage	*Patients*	*Per cent*
I	87	17.4
IIa	156	32.0
IIb	143	28.6
III	94	18.8
IV	20	4.0

Staging was according to the International Classification, but Stage II was subdivided into Stage IIa in which there was a fingerbreadth or more of clear space between the lateral induration and the pelvic wall and Stage IIb in which there was less. In order to be classified as a Stage III lesion, nodular extension out onto the pelvic

wall was required. A positive biopsy was obtained before a patient was allotted to Stage IV.

After the radium was inserted according to various modifications of the "Stockholm technique" and the vagina was tightly packed, measurements were made of dosage levels in the bladder and rectum with use of the Sievert ionization chamber.[6] This 0.3 c.c. ionization chamber is mounted on a curved probe which can be covered with a sterile sheath and inserted into the bladder and rectum. The instrument is calibrated to read in gamma roentgens per hour and under conditions of clinical use has an accuracy of ±10 per cent. It is standardized weekly by the department of radiophysics. With the patient under anesthesia and in the lithotomy position, measurements were recorded for 1 cm. intervals in the midline along the posterior portion of the bladder and the anterior wall of the rectum. During the period of this study, the radium insertions and vaginal packing were never changed because of high readings, since the purpose of the investigation was to determine the significance of such readings. In addition to the intracavitary radium, conventional x-ray therapy, usually with a 200 kv. machine, was given to the parametrium.

All 500 patients were followed until death or for at least 5 years. One patient left Sweden, but was followed at a university clinic elsewhere. Follow-up examinations were conducted at monthly intervals if the patients were symptomatic and at 3 month and then 6 month intervals if they were not. Some women who were chronically ill or who had reached the terminal stages of disease were unable to come to the clinic at the Radiumhemmet. These were followed by local gynecologists or physicians who sent detailed reports at intervals. The diagnoses appearing on all death certificates were confirmed by autopsy reports when these were available and otherwise by personal letters from their attending physicians. It is possible that some minor reactions were overlooked, but it is most unlikely that any major injuries were missed.

Results

The same principles of classifying injuries which were used in the preliminary paper have been followed here. It was found that the transient bladder and rectal symptoms which developed while the radium was in place or while the patient was undergoing external radiotherapy could not be correlated in any way with later radiation injuries and these have been omitted from further consideration. Symptoms developing within 3 months of death in patients clearly dying of carcinoma have generally been attributed to the underlying disease process rather than to radiation effect. Fistulas developing within one month of electroendothermy for recurrent or radioresistant disease have been considered to be due to the fulguration.

Once again rectal and bladder injuries have been divided into three groups according to severity. The Grade 1 injuries are those producing mild subjective symptoms after the completion of therapy accompanied by minimal objective changes in the mucosa. The criticism has been made that these are actually radiation *reactions* and not injuries and therefore should be omitted,[7] but they are included for completeness. It is conceded, however, that the continued impossibility of correlating these minor injuries with dosage, intensity, or any of the other factors to which the major injuries relate, supports the thesis that they are of little importance. In general they subside promptly.

Grade 2 injuries are those accompanied by moderately severe objective changes such as areas of necrosis, ulcers, or moderate stenosis, or those accompanied by protracted bleeding or pain. Classified as Grade 3 in-

Table I. Incidence of bladder and rectal injuries resulting from primary radiotherapy

	Bladder (%)	*Rectum (%)*
Grade 1	14.6	14.1
Grade 2	5.6	6.8
Grade 3	0.6	1.0

juries are the radiation fistulas and those rectal stenoses severe enough to require a colostomy. Differences in incidence between the previous preliminary report and this one represent for the most part additional injuries developing after that survey, although a few patients earlier classified as having serious injuries died soon thereafter and, in retrospect, their symptoms could be attributed to widespread dissemination of disease. These are no longer included among the injuries.

The over-all incidence of rectal and bladder injuries related to primary treatment is given in Table I. The 28 women considered as having Grade 2 bladder injuries include 18 described on cystoscopy as having a radiation reaction consisting of edema and erythema with occasional areas of necrosis, 4 with ulcers, 2 with papillomas of the posterior wall of the bladder, 3 with bladder stones, and 3 with severe, long-standing hematuria with minimal objective changes in the mucosa. Twenty-five of the 28 complained of frequency, burning, and urgency, and 19 of hematuria. There were 6 women who developed vesicovaginal fistulas. Three of these occurred in women who were heavily re-treated by irradiation for local recurrent disease. One was essentially terminal but developed more than 3 months prior to death. This and the 2 remaining fistulas have been classified as Grade 3 injuries resulting from primary treatment.

There were 34 patients who were classified as having Grade 2 rectal injuries. In 19 these were characterized by rectal induration and edema and in 14 by some degree of stenosis of the rectum or rectosigmoid. Two patients had rectal bleeding of a severity which required transfusion and these were considered serious on this basis alone. Twenty-seven complained of rectal bleeding, 13 had mucus in the stools, 11 diarrhea, 11 rectal pain, and 7 tenesmus. Eight patients developed rectovaginal fistulas, and 2 had rectal stenoses of a degree necessitating a colostomy. Five of these occurred, however, in patients who were heavily re-treated for recurrent disease. The other 5 which occurred as the result of primary treatment have been classified as Grade 3 rectal injuries.

The 3 patients who developed fistulas after the previous report are presented in detail below:

Case 1. A. J. was a 32-year-old para 0 originally treated for a large, ulcerating Stage IIb carcinoma of the cervix by means of a markedly increased radium dose; 180 mg. applied for 20 hours in the uterus and 162 mg. for 12 hours in the vagina. This was followed 3 weeks later by a routine treatment consisting of 52 mg. of radium in the uterus and 71 mg. in the vagina for 25 hours. The dose received by the bladder from the radium was more than 7,000 gamma r and, by the rectum, more than 5,000 gamma r. Initial external radiotherapy with a 200 kv. machine gave a skin dose of 2,000 r to each of two perineal, two anterior abdominal, and two posterior fields. Response was satisfactory, but 2 years later the patient was noted to have a recurrence for which she was treated with 50 mg. of radium applied intravaginally for 30 hours and 2,400 r external therapy to a large anterior and a large posterior field. Four months later she began to develop bladder symptoms and 6 months later was found to have both rectal and bladder fistulas. One year after the development of the fistulas the patient died of carcinoma.

Case 2. I. A., a 64-year-old para v with a late Stage II lesion, was treated initially with an increased intrauterine dose of 180 mg. of radium for 20 hours and an intravaginal box containing 70 mg. for 25 hours. The second treatment consisted of 55 mg. of radium in the uterus and 70 in the vagina for 25 hours. She was given 2,400 r skin dose to each of four fields, two abdominal and two back. Dosage measurements were incomplete. Nine months after treatment she developed a rectovaginal fistula as reported in the previous paper, and, 3 years later, a vesicovaginal fistula. After 5½ years her general health is good, and the rectal symptoms minimal, but she continues to have urinary incontinence.

Case 3. A. F., a 37-year-old para ii with a Stage IIb carcinoma of the cervix, was treated with 74 mg. of radium in the uterus and 88 mg. in a vaginal box for 25 hours followed 3 weeks later by an intrauterine dose of 62 mg. and an intravaginal dose of 96 mg. for 22 hours. The bladder received 4,910 gamma r and the rectum

2,815 during these treatments. A 2,800 r skin dose was given through each of four fields. One year later 40 μc of radiogold was injected into the left parametrium because of severe pain radiating into the leg. This improved but 2 years after the original treatment biopsy of an area near the rectum was positive, and extensive electrocoagulation was performed. Two years later, vaginal biopsy was again positive and the patient was re-treated with 76 mg. of radium packed against the area of metastasis and 3,500 r to a vulvar field given with the telecobalt unit. Within the next 2 months she developed both vesico- and rectovaginal fistulas. Fifteen months later the patient has a colostomy and continued leakage from the bladder, but is without evidence of disease.

The possibility of patients who have received radiation developing hydronephrosis and uremia solely on the basis of radiation reaction without evidence of recurrent disease has received increasing attention.[8-10] Traditionally, uremia has been considered by gynecologists to be due to recurrent disease and little effort has been directed toward diversion of the urinary stream. Routine intravenous pyelograms were not obtained after treatment in the patients in the present series except when the occurrence of symptoms directed attention to this system. Nothing, therefore, can be stated about the *incidence* of this complication, but 2 known cases of hydronephrosis, one necessitating nephrostomies, are presented in detail. It is planned to direct more attention toward the detection of this complication in the future.

Case 4. A. O., a 45-year-old para 0 with a Stage III cervical lesion extending to both pelvic walls and history of chronic pelvic inflammatory disease, was treated with an increased intrauterine dose of 200 mg. of radium for 20 hours and a vaginal dose of 70 mg. for 27 hours, followed 3 weeks later by a routine treatment of 62 mg. of radium in the uterus and 96 mg. in the vagina for 20 hours. The total measured bladder dose was 4,500 gamma r and rectal dose, 2,575 gamma r. This was followed by 3,600 r external therapy through back and abdominal fields. Two years after treatment she developed urinary tract symptoms and was found to have severe bilateral hydronephrosis. Bilateral nephrostomies were performed. Five years after the original treatment the patient is living and well but the nephrostomies are still required and a different type of urinary tract diversion is being considered.

Case 5. E. A. was a 54-year-old para ii with an early Stage II carcinoma of the cervix. The initial radium treatment consisted of 53 mg. in the uterus for 27 hours and 104 mg. in the vagina for 18 hours. This was followed in 3 weeks with 64 mg. in the uterus and 70 mg. in the vagina for 27 hours. Complete dosage measurements were not obtained. External radiation consisted of 2,000 r to each of four fields. Four years after treatment, she developed pyelonephritis and was found to have hydronephrosis on the left side. The infection responded to antibiotics and the patient is living without symptoms at the end of 5 years.

No patients in the current series developed evidence of necrosis of the hip and there were no small bowel injuries. In one patient, a serious radiation injury of the bowel was suspected because of severe rectal bleeding, but at autopsy she was found to have typical ulcerative colitis with the area of most marked change occurring in the transverse colon, well out of the field of radiation. It is, of course, possible that concern over the disease or, indeed, the treatment itself was indirectly responsible for the acute exacerbation of the colitis which caused death.

Correlation

The attempt to elucidate the predisposing factors in the etiology of radiation injuries led once again to the conclusion that Grade 1 injuries as defined in this study are of little significance because they are transient and cannot be correlated with dose, intensity, or any of the other factors to which the Grade 2 and Grade 3 injuries can be related. In most of the following tables, the Grade 2 and Grade 3 injuries are considered together in order to have a large enough group for statistical evaluation.

There were no fistulas in patients with Stage I tumors, confirming the impression that early lesions can be treated and cured with little risk of injury. There was a trend

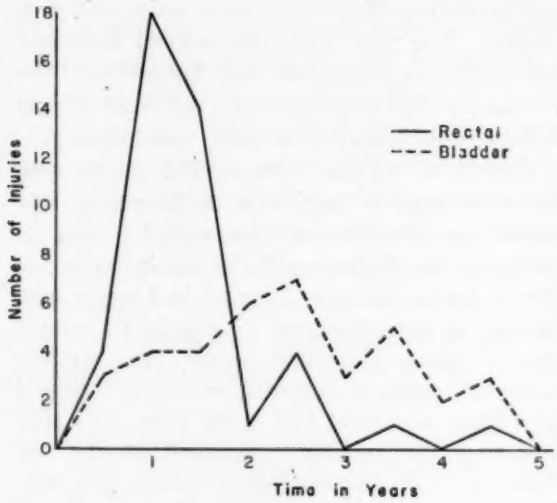

Fig. 1. The time of onset of symptoms related to severe bladder injuries compared to the time of onset of symptoms of rectal injuries.

toward increasing injury rates with increasing stage. Under the Stockholm system of individualization, the women with late Stage II and Stage III carcinomas receive significantly higher doses of radiation than do those with Stage I tumors so that this probably reflects an indirect correlation with dose.

Grade 2 and Grade 3 bladder injuries occurred in 15.3 per cent of the nulliparous women in the series compared with 6.2 per cent of all women studied. Perhaps the increased width of the vagina in the parous woman permits more effective distribution or packing of the radium. Serious bladder injuries increased slightly in women with a history of salpingitis (11.1 versus 6.2 per cent) and in postmenopausal women compared with premenopausal (8.6 versus 5.9 per cent). These factors did not affect the incidence of rectal injuries. There was no increase in either rectal or bladder injuries with stump lesions, with retroversion or retroflexion of the uterus or with the occurrence of fever during the treatment, but the effect of these was obscured by the fact that in such cases the radium dosage was routinely decreased. Neither a history of previous pelvic operation nor the type of applicator used seemed to influence the incidence of injury.

The previously established relationship between rectal injury and intensity of treatment was confirmed and extended to bladder injuries. The rate of serious injuries in 51 patients receiving more than 2,500 gamma r to the posterior wall of the bladder in less than 22 hours during a single treatment was 17.6 per cent compared to 9.0 per cent in 100 patients receiving the same dosage in 24 to 30 hours. Corscaden[11] has also demonstrated this effect.

One of the factors that was thought to be responsible for the recent increase in injury rate at the Radiumhemmet was the use of the higher intrauterine dose (up to 200 mg. of radium for 12 to 20 hours) in patients with late Stage II or Stage III tumors. When the injury rates in patients who received such an increased intrauterine dose are compared with those who had comparable lesions but received standard therapy, this is confirmed. The difference in incidence of rectal injuries (15.0 compared to 10.3 per cent) is greater than the difference in the incidence of bladder injuries (6.8 compared to 5.1 per cent).

Since the basic correlation which we are trying to establish with this series is that between dosage and injury rate, it is unfortunate that complete measurements were obtained in only 369 of the 500 patients. The omissions were the result of vagaries of both the ionization chamber and the house staff, but the fact that most patients were treated at least twice increased the opportunity for omission. The dose measured in the rectum is shown in Table II with corresponding injury rates. The *average* dose to the rectal mucosa from radium alone was 3,700 gamma r. The correlation with the Grade 1 injuries is essentially nonexistent, but the rate of serious injuries tends to increase with increasing dosage and is high when the dose is over 5,000 gamma r. If the dose from external radiotherapy is added to that measured in the rectum during radium therapy, as has been done in Table III, it is seen that there are no serious rectal injuries in patients who received less than 4,000 r total to the rectum and the injury rate rises

steeply over 6,000 r. The average total dose to the rectum in the patients of this series was 5,600 r. The narrow range between the dose being given and the apparent rectal tolerance under the conditions of treatment probably explains the relatively high injury rate in this group of patients.

Tables IV and V give the same relationships between dosage and bladder injuries. The average measured dose to the posterior wall of the bladder was 3,400 gamma r and the average total dose was 5,700 r. The bladder seems to be more resistant to injury than the rectum, but the injury rate was high when levels of more than 6,000 gamma r or 9,000 total r were reached. As might be expected, the correlation with total dosage is better than with that from radium alone.

Comment

The temporal distribution of the appearance of the Grades 2 and 3 rectal bladder injuries is given in Fig. 1. Most of the rectal injuries developed within the first 18 months and therefore the conclusions regarding rectal injuries drawn at the time of our preliminary report are valid. The peak incidence of development of bladder injuries proved to be between 2 and 3 years, however, so that a major proportion developed after that survey. The lag in appearance of bladder injuries was noted earlier by Twombly[12] and Albrecht.[13] No serious injuries were discovered more than 4½ years after treatment, even though most patients have been followed as long as 6 years, so that it seems unlikely that many additional lesions will develop.

There were 11 women with both serious rectal and serious bladder injuries. Five had fistulas involving both organs. Four of the 5 were patients who had been re-treated for recurrent disease, implying that overtreatment rather than extreme sensitivity to radiation was responsible. Three of these survived for 5 years, however, so the vigorous treatment of recurrence can be defended. A high incidence of complications following re-treatment was reported by McCormick.[14]

The various methods of re-treatment[4, 15, 16]

Table II. Rectal injuries correlated with dosage in gamma roentgens measured in the rectum

Gamma r	*No. of patients*	*Grade 1 injuries (%)*	*Grades 2 and 3 injuries (%)*
0-1,999	23	17.3	4.3
2,000-2,999	91	19.7	4.3
3,000-3,999	122	15.5	9.8
4,000-4,999	71	12.6	14.0
5,000-5,999	47	17.0	21.0
6,000 and over	14	14.2	21.0

Table III. Rectal injuries correlated with total radiation

Roentgens	*No. of patients*	*Grade 1 injuries (%)*	*Grades 2 and 3 injuries (%)*
0-3,999	45	15.6	0.0
4,000-4,999	95	17.9	8.4
5,000-5,999	91	12.1	7.7
6,000-6,999	69	17.4	20.3
7,000-7,999	46	13.1	17.4
8,000 and over	23	17.4	26.1

Table IV. Bladder injuries correlated with dosage in gamma roentgens measured in the bladder

Gamma r	*No. of patients*	*Grade 1 injuries (%)*	*Grades 2 and 3 injuries (%)*
0-1,999	54	11.1	3.7
2,000-2,999	102	15.6	3.9
3,000-3,999	93	11.8	6.4
4,000-4,999	57	22.8	10.5
5,000-5,999	40	17.5	2.5
6,000 and over	16	6.2	31.2

Table V. Bladder injuries correlated with total radiation

Roentgens	*No. of patients*	*Grade 1 injuries (%)*	*Grades 2 and 3 injuries (%)*
0-3,999	61	11.5	1.6
4,000-4,999	69	13.0	7.2
5,000-5,999	88	13.6	5.7
6,000-6,999	65	13.8	7.7
7,000-7,999	46	13.0	6.5
8,000-8,999	21	19.0	9.5
9,000 and over	17	11.8	29.4

Table VI. Injury and 5 year survival rates in patients re-treated because of recurrent or persistent disease

Mode of re-treatment	*No. of patients*	*No. surviving*	*No. of serious injuries*
Fulguration	27	7	1
Fulguration and radium	6	1	2
Fulguration and x-ray	5	0	1
X-ray and Co^{60}	24	8	4
Radium	16	3	3
X-ray and gold	10	2	1
Radioactive gold	6	2	0
Surgery	7	2	0
Surgery and radiation	2	0	0
Surgery and radiation and fulguration	1	0	0
Total	104	25	12

Table VII. Five-year survival rates (500 cases)

	No. of cases	*% survival*
Stage I	87	89.7
Stage II	299	53.6
IIa	156	66.0
IIb	143	40.5
Stage III	94	38.2
Stage IV	20	5.0
All stages		54.5

used at the Radiumhemmet during the 5 years of this survey and their contribution both to survival rates and injury rates can be ascertained from Table VI. One hundred four of the 500 were re-treated in some manner, and, of these, 25 survived 5 years. All patients with survival credited to fulguration or to re-treatment with radium had recurrent local tumor proved by positive biopsy. In some cases, however, radioactive gold or additional external therapy was given to patients with pain in whom a tissue diagnosis of recurrent or metastatic disease could not be established. It would appear that vigorous treatment of certain patients with proved or suspected recurrent or persistent disease has played a part in the improved over-all survival rate and that the price in resulting injuries, although high, is not exorbitant.

The most important factor in the production of radiation injuries seems to be *total* dosage. It will be seen from Tables III and V that when the total dose in the rectum was less than 4,000 r there were no serious rectal injuries and that when the total bladder dose was under this level the incidence was only 1.6 per cent. Correlation with stage and with increased intrauterine dose in advanced cases reflects the effect of total dosage indirectly. It is now the policy at the Radiumhemmet to measure all rectal and bladder dosages at the time of radium insertion using 4,000 gamma r to an area of more than 2 cm. in diameter in the rectum as the usual maximum permissible dose and reducing the time of treatment or repacking the vagina in cases where it appears that this will be exceeded. In those cases in which the tumor extends onto the posterior wall of the vagina as well as in some late lesions, the dose may be increased provided that the tumor has responded well to the first treatment.

The other factor of considerable importance in the production of radiation injuries is the intensity of treatment. The increased survival rates at the Radiumhemmet in the more advanced lesions is considered to be the result of the very intensive radiation given by the increased intrauterine radium treatment, but the current policy is to permit delivery of no more than 2,400 gamma r to the rectum in 24 hours. It is hoped that the slight lowering of dosage and intensity will permit a reduction in serious injuries without a decrease in cure rates. There are occasional injuries that cannot be explained on the basis of our current knowledge and these remain, for the moment, unpreventable.

The role which an instrument to measure dosage in the bladder and rectum at the time of radium insertion can play in the reduction of injuries is only now being established. Although many institutions are currently making such measurements, there are relatively few where a significant number of patients have been followed for a long enough time to give useful data on the

correlation of dosage with injuries. Fletcher[17] has recently reviewed the literature on this problem. Some physicists maintain that the data obtained from isodose curves for a given method are more useful than the individual measurements. Such curves are available for the various patterns of radium insertion used at the Radiumhemmet,[18] but when a given pattern of radium insertion is analyzed for variation in rectal and bladder measurements the range from one patient to another is found to be as much as 80 r per hour. Anatomic variation and differences in technique of packing the vagina alter the distribution in the individual patient profoundly.

No tabulation of the complications of a method should be offered without presenting the results of the method. The 5 year survival rate for the 500 cases analyzed here is given in Table VII. The follow-up, as previously stated, was 100 per cent. The results have not been corrected for death from intercurrent disease. It should be remembered that this series extends from mid-1953 to mid-1954 and that the survival rates will not correspond exactly with those published from the Radiumhemmet for either calendar year.

It is important to follow the patients to whom radiation injuries have been ascribed and discover what the ultimate resolution of these problems has been. The 5 year end results of rectum and bladder injuries including those resulting from re-irradiation are given in Tables VIII and IX. Of 127 patients with rectal symptoms attributed to initial treatment or to re-treatment, 5 continue to have occasional rectal bleeding, 3 have rectal stenosis without symptoms, and 2 are living with colostomies. Of 100 patients with bladder symptoms attributed to radiation treatment, 6 continue to have occasional hematuria and 2 are living with vesicovaginal fistulas. In addition, there is one patient with bilateral nephrostomies because of fibrosis of the ureters. Thus, of 273 women surviving more than 5 years after receiving radium and external therapy for cervical carcinomas, 5 or 1.9 per cent continue to have serious problems as a result of treatment.

Summary

Five hundred patients with invasive carcinoma of the cervix treated at the Radiumhemmet have been followed for more than 5 years with particular attention to the development of radiation injuries. It appears that the increased dosage of radiotherapy used on an experimental basis during the time of this study has been responsible for improvement in survival rates but has been accompanied by a higher rate of injuries.

There is a direct correlation between dosage levels in bladder and rectum and injury rate. Under the conditions of treatment at the Radiumhemmet, a dose of more than 5,000 gamma r or a total dose of more than

Table VIII. Rectal injuries—5 year end results

Grade 1		*79*
No further symptoms	52	
Died	24	
Occasional rectal bleeding	3	
Grade 2		*38*
No further symptoms	20	
Died	14	
Continuing stenosis without symptoms	3	
Occasional rectal bleeding	1	
Grade 3		*10*
Died	7	
Living with colostomy	2	
Living with minimal symptoms	1	

Table IX. Bladder injuries—5 year end results

Grade 1		*67*
No further symptoms	41	
Died	23	
Occasional bleeding	3	
Grade 2		*29*
No further symptoms	19	
Died	7	
Continuing symptoms	3	
Grade 3		*6*
Died	4	
Living with fistulas	2	

6,000 r to the rectal mucosa is accompanied by a very high injury rate as is a dose of more than 6,000 gamma r or more than 9,000 total r to the bladder. Because of the investigation reported here, treatment of carcinoma of the cervix, beginning in 1956, has been modified on the basis of direct dosage measurements in the bladder and rectum at the time of treatment. Currently 4,000 gamma r to an area of more than 2 cm. in diameter is considered the maximum permissible dose in the average patient. There is also a correlation between intensity of treatment and injury rate in both the bladder and rectum. A total of 2,400 gamma r to the rectum in 24 hours is the maximum intensity which is now permitted.

Both rectum and bladder injuries are usually transient, with those in the rectum generally occurring sooner than those in the bladder. The incidence of permanent disability due to therapy in this series (one per cent of patients treated) is very low compared to the over-all 5 year survival rate of 54.5 per cent. Fear of radiation injuries should not deter the gynecologist from radiotherapy as the method of choice in treatment of carcinoma of the cervix.

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Prevalence of carcinoma arising in cervical stumps

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SINCE Alterthum[1] in 1895 published the first report of carcinoma arising in cervical stumps, the question as to whether there is a greater risk of carcinoma developing in a cervical stump than in an intact uterus has remained unsettled. Despite this uncertainty, many surgeons believe that the incidence of carcinoma is actually higher in the cervical stump.[3] The major obstacle to the solution of the problem has been the absence of suitable control groups from which one could determine what the expected number of carcinomas should be. Thus, even though several studies have been conducted in which sizable groups of women who have had subtotal hysterectomy have been followed for subsequent development of cervical carcinoma, there was no accurate way of estimating what the expected incidence of cervical cancer would be if the body of the uterus had not been removed.

Many factors influence the incidence of cervical cancer, such as age, marital status, parity, socioeconomic status, and racial and ethnic background.[5, 11] For example, cervical cancer is more prevalent among older women, among women of lower socioeconomic status, among the married as compared to the unmarried, and in multiparous as compared with nulliparous women. It is rare among Jewish women. These factors and possibly others, as yet unknown, may account for the varying incidences reported from different geographic areas. Thus, any group of women studied for the incidence of cervical carcinoma represents a unique group which can be compared to other groups only if the above variables are properly controlled or weighed.

In published articles dealing with cancer of the cervical stump the term "incidence" is often used in two different ways, neither of which reflects "incidence" in the strict epidemiologic sense. Some authors use "incidence" to denote the number of cases found at a given time in a group of patients studied. This is actually "prevalence."* Others use "incidence" to give the ratio of the number of women with cancer of the cervical stump with respect to the total number of cases of cervical cancer of all types seen in their experience. Such "incidences," differently defined, have then been compared with each other and also with the prevalence of cervical cancer among women in the population at large. Obviously, such comparisons cannot provide any answers that are statistically valid.

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A preliminary report of these data was presented at the Seventh Annual Meeting of the Inter-Society Cytology Council, Detroit, Michigan, Nov. 19, 1959.

*The "incidence rate" for a specific disease is the ratio of the number of new cases of the disease which develop during one year to the population at that time. The "prevalence ratio" of a specific disease is the ratio of the number of cases of the disease known to exist at a given time to the population at the same time.[6] "Incidence," therefore, refers to the rate at which a disease is developing, while "prevalence" reflects what proportion of a population has the disease at a certain time.

Pearse[9] traced 1,040 patients 5 or more years following subtotal hysterectomy by questionnaire and state health registries. He found cervical cancer had developed in 1.01 per cent. He noted that the percentage (1.99) of cancers in cervical stumps of 201 women whose hysterectomy was performed for inflammatory disease was twice that (0.97) of a group of 410 women whose operation was for leiomyomas. These data have been erroneously credited to Monod by Blaikley.[3]

Monod[7, 8] actually was one of the first to affirm that women who have had a subtotal hysterectomy have the same chance of developing cancer of the cervix, no more and no less, as women who have had no surgical treatment at all. Pearse[9] has credited Monod with statements to the contrary.

Scheffey[10] found cervical cancer in 0.9 per cent of 554 women 6 to 21 years after subtotal hysterectomy. Scheffey's findings were based on physical examinations supplemented by correspondence with some members of the group.

Thornton, Claiborne, and Jones[13] obtained follow-up data on 781 patients with cervical stumps. Ninety-five of these patients had died. Of the 686 living, 306 were examined and information on the remaining 380 was obtained by interview. Cervical carcinoma was found in 6 women within 2 years after subtotal hysterectomy; the authors, therefore, assumed that the tumor was present at the time of operation. In only 2 women did cervical carcinoma develop 2 or more years after subtotal hysterectomy.

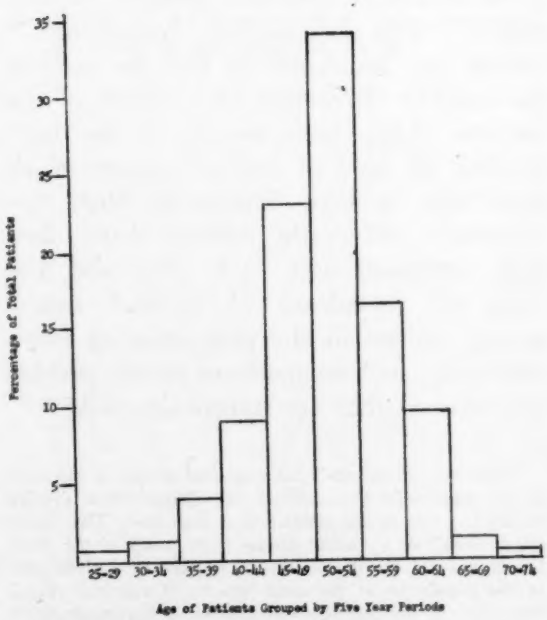

Fig. 1. Identical age distribution for both test and control groups.

Since none of the studies cited above included an identical group of women without subtotal hysterectomy to serve as controls, one does not know what the expected occurrence rate would have been if subtotal hysterectomy had not been performed. Unfortunately, none of these authors indicate a population profile from which one might estimate the expected number of cancers. Thus, we cannot tell from these studies whether or not the cervical stump constitutes a special hazard in the later development of cervical cancer.

This uncertainty is expressed by Johnson,[4] who stated that "there are, unfortunately, no trustworthy figures on the incidence of carcinoma of the cervical stump" and by TeLinde,[12] who wrote that "the incidence of the development of carcinoma of the cervical stump can only be estimated."

Exfoliative cytology has afforded a useful method of determining the prevalence of cervical cancer in a given population. A vaginal cytology screening program is being conducted in Philadelphia by the Woman's Medical College of Pennsylvania in cooperation with the Cytology Section of the National Cancer Institute. Since epidemiologic information is obtained from each patient in this survey, we had the opportunity of comparing the prevalence of carcinoma of the cervix in women who have cervical stumps with the prevalence found in a comparable group of women with intact uteri.

Method

In this program all patients screened were actively employed in some local industry or business and were essentially asymptomatic. In each case two slides were prepared for cytologic study from vaginal aspirates. A brief gynecologic history was obtained as

well as certain additional information such as age, marital status, race, and socioeconomic background.

Patients were asked about previous surgical operations involving pelvic organs. If it appeared that a hysterectomy, either total or subtotal, had been performed, the operative and surgical pathology reports from the respective hospitals were reviewed. It was commonplace to find that the patients did not know the exact nature of the operation. Many were under the impression that they had had a total hysterectomy when in fact a cervical stump remained.

Among the first 20,000 women screened in the over-all program, 1,793 indicated they had had previous uterine surgical operations. We were able to obtain surgical pathology and operative records for 1,384 of these: 314 had had a subtotal hysterectomy; 932 had had a total hysterectomy; and 138 had actually had no hysterectomy at all but some other operative procedure. Thus, we collected 314 cases in which a subtotal hysterectomy had been performed 2 or more years previously, confirmed in each case by reviewing the operative and surgical pathology reports from the respective hospitals.

A control group for the purpose of comparison was assembled as follows: For each patient with a cervical stump we picked the next 2 patients with intact uteri who (1) followed chronologically in our general survey, and (2) exactly matched the cervical stump patient with respect to age, marital status, race (white or Negro), and whether Jewish or non-Jewish. Each of these factors has been shown to influence the prevalence of carcinoma of the cervix. Thus, for each woman with a cervical stump in the test group, there were in the control group 2 women with an intact uterus and an identical epidemiologic profile.

All patients in both test and control groups in whom the result of the cytologic test was suspicious or positive were subsequently studied by cervical scrapings and biopsy. Final diagnoses reported in this study were based on histopathologic examination of the biopsy specimens.

Table I. Epidemiologic profile of the group of women with cervical stumps and of the control group

	Women with cervical stumps	*Control group*
No. in group	314	628
Mean age	52	52
Per cent married	84.4	84.4
Of married women per cent nulliparous	28.3	22.7
Of parous women, mean parity	2.1	2.2
Per cent white	72.6	72.6
Per cent Negro	27.4	27.4
Per cent Jewish	12.4	12.4

Results

Because of the special method of selecting the control group the following factors were identical in both groups: age distribution and the ratios of married to single, white to Negro, and Jewish to non-Jewish women. As seen in Table I the mean age of each group was 52 years. The age distribution is illustrated in Fig. 1. In each group, 15.6 per cent of the women were unmarried and 84.4 per cent were married. Of the married women 22.7 per cent of the control group were nulliparous and 28.7 per cent of the cervical stump group were nulliparous. The mean parity was 2.2 and 2.1 per parous woman in the control and test groups, respectively. In each group 72.6 per cent of the women were white and 27.4 per cent were Negro; 12.4 of the women were Jewish in both control and test groups. All patients in the subtotal hysterectomy group had been operated upon at least 2 years previously; the mean postoperative time interval was 13.6 years.

The pathologic diagnoses reported at the time of subtotal hysterectomy are given in Table II. Leiomyomas were present in 75.2 per cent of the cases.

The cytologic and subsequent biopsy findings are summarized in Table III. Of the 314 women with cervical stumps, there were 6 (1.9 per cent) with suspicious or positive smears, 3 (0.95 per cent) with invasive squamous carcinoma, 1 (0.32 per cent) with

intraepithelial carcinoma, and 2 cases (0.64 per cent) with benign epithelial atypism. Of the 628 women of the control group there were 11 (1.8 per cent) with suspicious or positive smears, 6 (0.95 per cent) with invasive carcinoma, 1 (0.16 per cent) with intraepithelial carcinoma, and 4 (0.64 per cent) with benign epithelial atypism. There is no statistically significant difference between the control and test groups with regard to (1) the percentage of suspicious and positive smears, and (2) the percentage of either invasive or intraepithelial carcinomas.

Comment

To the best of our knowledge, the present study represents the first instance in which the prevalence of carcinoma of the cervix was determined simultaneously in a group of women who had had subtotal hysterectomy and in a control group with intact uteri. Both groups had an identical epidemiologic profile and were studied by both cytology and biopsy. The design of this study has thus avoided the pitfalls of earlier studies in which there was no adequate control group for comparison. Under the conditions of our study there was no statistically significant difference between the two groups with regard to (1) the percentage of suspicious and positive cytology smears or (2) the percentage of either invasive or intraepithelial carcinomas demonstrated by biopsy. Our results indicate that the presence of a cervical stump does not of itself alter the risk of the development of cervical carcinoma at a later date.

There has been a wide variation in the reported prevalence of carcinoma arising in cervical stumps[2]; this is probably due to differences in the types of population studied by the various investigators. Future studies should, therefore, include suitable control groups.

In Pearse's[9] study on women with cervical stumps, the prevalence of cervical carcinoma was twice as high in women whose hysterectomy had been performed for inflammatory disease as it was in women whose hysterectomy was done for the presence of leiomyomas. Unfortunately, our study throws no light on this problem, because there were too few cases to permit a valid statistical appraisal.

Table II. Pathologic diagnoses in 314 cases at the time of subtotal hysterectomy

A. Leiomyomas		236
With endometrial hyperplasia	15	
With endometrial polyps	9	
With leiomyosarcoma	1	
With cervical polyps	3	
With normal intrauterine pregnancy	1	
B. Endometrial hyperplasia (including the 15 in A)		24
C. Endometrial polyps (including 9 in A)		11
D. Adenomyosis		7
E. Cesarean hysterectomy		4
F. Associated ectopic pregnancy		2
G. Associated tubal or ovarian diseases (mostly inflammatory)		21
H. No abnormalities noted		33

Table III. Cytologic and biopsy diagnoses in the two groups*

	Women with cervical stumps		*Control group*	
	No.	*%*	*No.*	*%*
No. in group	314		628	
No. with suspicious or positive smears	6	1.9	11	1.8
Biopsy findings				
Benign epithelial atypism	2	0.64	4	0.64
Intraepithelial carcinoma	1	0.32	1	0.16
Invasive squamous carcinoma	3	0.95	6	0.95
Total carcinomas	4	1.27	7	1.11

*By the chi-square test there was no significant difference between the two groups with respect to the above percentages for each item.

Summary

The prevalence of carcinoma of the cervix was studied simultaneously in a group of women with cervical stumps (314) and in a control group with intact uteri (628), both groups having an identical epidemiologic profile. The women in both groups were initially screened by vaginal cytology and all patients with suspicious or positive smears were studied further by cervical scrapings and biopsy. No statistically significant difference was found between these two groups with respect to (1) the percentage of suspicious and positive cytologic smears, and (2) the percentage of either intraepithelial or invasive carcinomas. Our studies indicate that a woman with a cervical stump has the same chance, no more and no less, of developing a carcinoma of the cervix, as a woman with an intact uterus, all other factors being equal, such as age, marital status, parity, and racial and ethnic background.

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Serum protein alterations in gynecologic diseases, with special reference to cancer of the uterine cervix

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ALTHOUGH it has been generally conceded by investigators[3-6, 13, 14, 16, 17, 20, 23] that decrease of albumin and increase of globulin are constant changes in the sera of cancer patients, particularly in advanced cases, opinions are divided as to which changes of the fractions[1, 2, 11, 14, 15, 18-21] are clinically significant. Considering the lack of definite information on this problem, the present study was conducted to discover whether or not any peculiarities exist in the electrophoresis of serum of patients with uterine cancer, as compared with the normal and nonmalignant group, and, if so, whether or not they are correlated with the diagnosis, treatment, or prognosis of the disease.

Methods and materials

It has been shown by many investigators[22] that the horizontal strip method as a zone electrophoresis is almost equal to Tiselius techniques in accuracy, and has the virtue of simplicity. Paper electrophoresis was performed for 5 hours with 7.5 Ma. at pH 8.6, with veronal buffer, using Toyo filter paper No. 51 (corresponding with Whatman No. 1) in Kobayashi's apparatus,[12] which was composed of two parts—densitometer and compartments, which were connected by plastic tubing to facilitate leveling of the buffer. After the paper strips were dried for 20 minutes at 100° C., they were stained with Amidoschwarz 10 B and read through densitometer. The specimens were obtained from normal women, patients with nonmalignant gynecologic lesions, and those with uterine cancer in different stages, both treated and nontreated, and other cases of gynecologic malignancy.

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Results

1. Paper electrophoresis of the serum of normal women. The serum electrophoresis of 20 normal, nonpregnant women is demonstrated in Table I. As the table shows, the albumin of the Chinese woman shows a lower value than that of the Japanese[12] and also probably lower than that of the Caucasian as reported in literature,[22] while the other fractions show no significant difference.

2. Paper electrophoresis of the serum of patient with nonmalignant gynecologic disease. Thirty patients with nonmalignant gynecologic conditions comprising 5 cases each of uterine fibroid, ovarian cyst, endo-

crine diseases, genital tuberculosis, pelvic inflammation, and cervicitis with erosion show the pattern of paper electrophoresis as given in Table I.

Compared with the normal woman, this group shows a significant decrease of albumin and increase of α_1- and γ-globulin but no significant change in α_2- and β-globulin.

3. Paper electrophoresis of the serum from patients with uterine cancer.

A. Comparison of serum proteins of uterine cancer patients with those of normal women. As Tables I and II demonstrate, Stage III and IV cases show significant changes in each fraction, whereas Stage I and II cases show significant differences only in albumin and γ-globulin, as compared with the serum of normal females.

B. Comparison of uterine cancer cases with nonmalignant gynecologic diseases. As Tables I and II show, compared with nonmalignant gynecologic diseases, Stage I and II uterine cancer cases reveal no significant change in albumin and γ-globulin fraction and only slight but significant changes in α_1- and β-globulin, whereas Stage III and IV uterine cancer cases show significant differences in albumin, α_2-, and β-globulin.

C. Comparison of Stage I and II with III and IV uterine cancer cases. As Tables I and II demonstrate, there are significant changes in albumin, α_1-, and α_2-globulin but no significant difference in β-globulin and γ-globulin fractions between the two groups. From Table I, another interesting finding should be noted, namely, in Stage I and II cases β-globulin is greater than α_2-globulin, whereas, in Stage III and IV cases α_2-globulin exceeds β-globulin. Therefore, the ratio of α_2- to β-globulin is below 1.0 in the former and above 1.0 in the latter.

4. Serum electrophoresis of the nonmalignant cachectic patients. A few patients suffering from cachexia due to nonmalignant disease including liver cirrhosis, arteriosclerosis, and tuberculosis were tested with serum electrophoresis. The pattern was shown as follows: Albumin, 32.9; α_1-globulin, 5.9; α_2-globulin, 10.5; β-globulin, 13.0; and γ-globulin, 37.9. The ratio of α_2- to β-globulin was below 1.0.

5. Serum electrophoresis of women, particularly with pelvic malignancies exclusive of uterine cancer. This group comprises 10 cases of vulvar cancer, 2 of ovarian, 3 of breast, 1 of bladder, 2 of urethral, 1 of rectal, 2 of vaginal, and 1 case of uterine

Table I. Patterns of paper electrophoresis of serum proteins (per cent of total protein)

Group	No. of cases	Albumin	Globulin				α_2/β
			α_1	α_2	β	γ	
Nonmalignant	30	46.07	5.23	9.02	12.93	26.75	0.70
Stage I-II uterine cancer (before treatment)	31	47.65	4.60	8.60	12.18	26.98	0.71
Stage I-II uterine cancer (after treatment)	34	47.15	4.91	9.10	12.69	26.13	0.71
Stage III-IV uterine cancer (before treatment)	17	41.27	5.76	12.87	10.85	29.20	1.19
Stage III-IV uterine cancer (after treatment)	14	43.98	4.32	9.71	12.31	29.65	0.79
5 year survivals	7	44.04	5.39	8.35	12.25	29.96	0.68
Normal (Chinese)	20	52.42	3.95	8.57	12.40	22.66	0.69
S.D. ($\sqrt{u^2}$)		3.03	1.21	1.53	1.70	3.24	0.15
99 per cent range (Average × 2.5 S.D.)		44.84-60.00	0.92-6.95	4.74-12.40	8.15-16.65	14.86-30.75	0.32-1.07
Normal (Japanese) (Kojima)	10	55.40	3.40	7.80	11.70	21.70	0.67
S.D.		1.68	0.62	0.93	0.81	1.12	0.13

sarcoma. Twenty-two cases were divided into A and B Groups, the former including cases where the lesion was localized in the primary organ, and the latter, the cases where the lesion extended beyond the primary organ. As Table III shows, there is the same trend between the early (Group A) and the advanced (Group B) and between the treated and the nontreated groups, as between the uterine cancer groups.

6. Therapeutic response as reflected in pattern of paper electrophoresis of serum protein in uterine cancer cases. The therapeutic response was well demonstrated in the change of paper electrophoresis of Stage III and IV uterine cancer cases but not of the Stage I and II cases. As Table I illustrates, before treatment the Stage III and IV uterine cancer cases show high α_2-globulin exceeding β-globulin, and after treatment α_2-globulin is greatly diminished and β-globulin consequently exceeds α_2-globulin, regaining the normal pattern, although β-globulin shows only a relative but nonsignificant increase. α_1-globulin also shows a significant decrease but less marked compared with α_2-globulin. Albumin and γ-globulin do not show any significant change as a response to therapy. Such changes of albumin and γ-globulin caused by the progress of the cancer seem to be irreversible, as is well depicted in Tables I and II, where still significant decrease of albumin and increase of γ-globulin are seen in relatively or absolutely cured cancer patients. As far as the therapeutic response is concerned, in the majority of advanced cases the normal ratio of α_2- to β-globulin was restored after treatment, regardless of whether irradiation or operation was used. There are, however, some cases where the ratio fails to return to normal as will be demonstrated with illustrative clinical cases.

A. Case where the ratio returned to the normal range after treatment.

Case 1. Patient U. T. H., 33 years old, bore her first child at 19. She was first examined in April of 1957, at which time the clinical diagnosis was Stage I cervical cancer and the pathologic diagnosis was epidermoid cancer. She had

Table II. Significance of difference between groups*

Group	Albumin	Globulin			
		α_1	α_2	β	γ
Normal, nonmalignant	S	S	NS	NS	S
Normal, Stages I-II	S	NS	NS	NS	S
Normal, Stages III-IV	S	S	S	S	S
Nonmalignant, Stages I-II	NS	S	NS	S	NS
Nonmalignant, Stages III-IV	S	NS	S	S	NS
Stages I-II and Stages III-IV	S	S	S	NS	NS
Before and after treatment Stages III-IV	NS	S	S	NS	NS
Normal, treated Stages III-IV	S	NS	NS	NS	S
Normal, 5 year survival	S	S	NS	NS	S

*S = significant; NS = nonsignificant.

Table III. The change of paper electrophoresis after treatment of pelvic malignancy

	Case No.	Albumin	Globulin				α_2/β
			α_1	α_2	β	γ	
No treatment							
Group A	5	45.2	5.0	9.5	14.3	26.0	
Group B	8	38.0	6.3	13.4	10.3	32.0	
Total	13	40.8	5.8	11.9	11.8	29.7	1.01
After treatment	9	43.4	5.7	9.5	12.1	29.3	0.79

Table IV. Paper electrophoresis of serum protein of patient U. T. H.

Date	Albumin	Globulin				α_2/β	Remarks
		α_1	α_2	β	γ		
On admission, Aug. 29, 1957	33.5	7.5	11.0	9.6	38.4	1.15	Hemoglobin 45 per cent; R.B.C. 1.31 million; sedimentation rate 103.5; necrotic cervix, frozen pelvis, high fever
2 months after admission	33.8	4.4	7.1	13.7	41.0	0.52	X-ray deep therapy completed; parametrial infiltration and cervical tumor dramatically retrogressed
3 months after admission	35.1	5.8	7.8	14.3	37.0	0.55	Radium therapy completed, pelvis returned to normalcy

Table V. Paper electrophoresis of serum protein of patient S. T. Y.

Date	Albumin	Globulin				α_2/β	Remarks
		α_1	α_2	β	γ		
July 20, 1957 (20 months after operation)	51.5	3.8	11.5	13.9	19.3	0.83	Sedimentation rate 38 Biopsy, no malignancy
Aug. 20, 1957	49.0	5.1	14.3	10.7	20.9	1.34	Sedimentation rate 37 Epidermoid cancer recurrent found at left vaginal stump
Sept. 3, 1957	45.8	7.4	15.3	10.0	21.5	1.53	Sedimentation rate 54 3,350 mg.hr. radium applied; neuralgia and tenesmus increased, left parametrial infiltration remarkable
Nov. 28, 1957	42.7	7.3	15.5	12.7	21.8	122	12,000 r. deep x-ray irradiated; no improvement in general and local findings
Dec. 19, 1957	39.7	5.7	13.4	11.5	29.7	1.17	Greenhill's technique for intolerable neuralgia

evaded our treatment until August 29, the same year, when she was transferred to our ward in a very critical condition, as evidenced by severe neuralgia, high fever, edema of the legs, marasmus, enlarged necrotic cervix, frozen pelvis, etc. The electrophoresis on successive follow-up examinations is recorded in Table IV. The patient was discharged in excellent condition on Nov. 26, 1957, and is still doing well (Fig. 1).

B. Case where the pattern of serum electrophoresis did not return to normal range.

Case 2. S. T. Y., aged 47, para viii, underwent an Okabayashi operation on Nov. 18, 1956, for Stage II uterine cancer (epidermoid cancer). The postoperative course was uneventful. On July 20, 1957, she returned for follow-up, when a small induration was noted at the vaginal stump. Biopsy revealed no definite malignancy. Serial tracings of serum electrophoresis are recorded in Table V. The patient died on Feb. 7, 1958, from azotemia (nonprotein nitrogen level 158 mg.) (Fig. 2).

7. Evaluation of the ratio of α_2- to β-globulin as an indicator of prognosis of uterine cancer. Since the ratio of α_2- to β-globulin usually deviates from the normal pattern only in advanced uterine cancer as demonstrated in Section 3 under Methods, and there are two types of response of uterine cancer to treatment as manifested in the change of the ratio, this ratio would seem very significant in the prognostication of the disease. We attempted to prove this assumption by following up 181 patients with

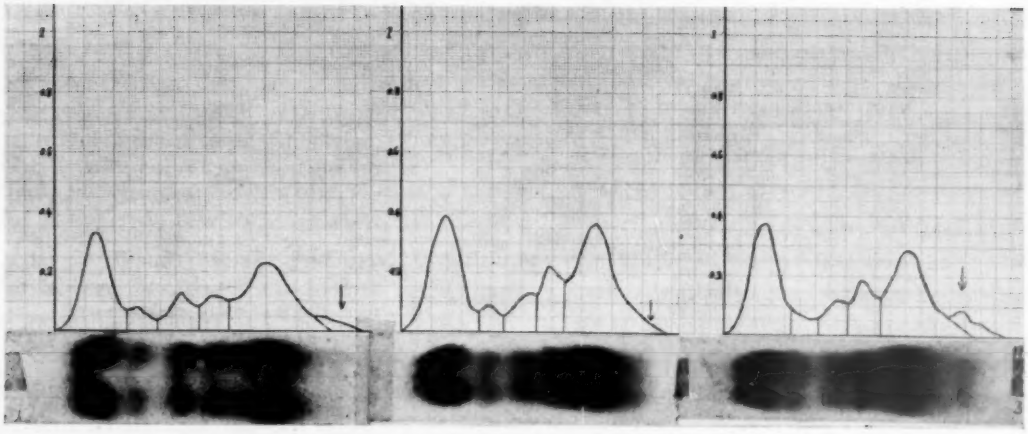

Fig. 1. Paper electrophoresis of serum protein in Patient U. T. H., in whom a favorable therapeutic response was reflected in the return of the abnormal ratio of α_2- to β-globulin to the normal.

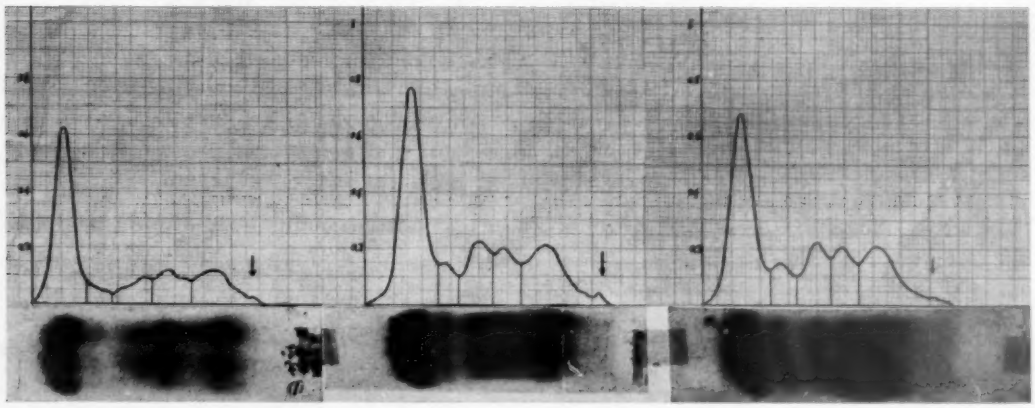

Fig. 2. Paper electrophoresis of serum protein in Patient S. T. Y., in whom an unfavorable therapeutic response was reflected in the persistent abnormal ratio of α_2- to β-globulin.

uterine cancer (and pelvic malignancies), who were tested with serum electrophoresis before June 30, 1958, and whose follow-up examination was started on Sept. 1, 1958, and accomplished on 139 cases (77.3 per cent). On the basis of our experience, we have tentatively set the limit between the normal and abnormal ratio at 1.0; the ratio below 1.0 was referred to as normal and the ratio including and above 1.0 as abnormal (or reversed) ratio. As Table VI indicates, of 52 patients with abnormal ratios 26 were dead (50 per cent), whereas of 87 patients with normal ratios only 4 were dead (4.6 per cent). Should the patients whose prognosis was proved to be hopeless and who were at the point of death be included, the group with abnormal ratios would show a mortality rate of 63.4 per cent (33 cases) and the normal ratio group 5.7 per cent (5 cases). The difference between the two groups is apparently significant. When the cases were classified into 3 groups, beyond one year (the longest 14 months), 6 to 12 months, and under 6 months (the shortest 2 months), according to the periods dating back to the time of electrophoresis (up to the time of follow-up), it was anticipated that the mortality rate increased in proportion to the time elapsed; however, we can see a statistically significant difference of mortality rate between the normal and abnormal ratio groups at various periods of follow-up. In Table VII were

included in parentheses the hopeless cases in which death seemed inevitable in the near future at the time of follow-up examination.

8. Can the ratio of α_2- to β-globulin be used in the diagnosis of pelvic malignancy? As far as the diagnosis of uterine cancer is concerned, it is well recognized that biopsy is the most reliable and accessible procedure and no auxillary procedures other than the Papanicolaou test are needed. However, as far as deep-seated recurrent uterine cancer or encapsulated ovarian malignancy is concerned, the diagnosis is based entirely on indirect findings or needle biopsy, which is not advisable from the clinical point of view. The abnormal ratio of α_2- to β-globulin, which may be not specific but is almost constantly present in advanced pelvic malignancies, suggests a possible change in the diagnosis of the condition.

Case 1. The patient was a 62-year-old gravida 0, para 0, whose menopause started at the age of 50. Since November, 1956, she had suffered from abdominal distention and had undergone paracentesis seven times, each tap resulting in 400 to 700 c.c. of fluid. Laboratory data in October, 1957, at University Hospital included: Takata reaction 6 tubes plus; icterus index 18; Van den Bergh test—direct, delayed, indirect, plus; thymol turbidity test 2.0; alkaline phosphatase 10.0 μ; urobilinogen 3-plus; protein in urine, 1-plus. The diagnosis at that time was liver cirrhosis. She was transferred to our clinic on Oct. 30, 1957, at which time she was in a cachectic condition, with marked pitting edema of the legs. The abdomen was of the size of a 10 months' pregnancy. There was no sign of ascites or of hydrothorax. The findings were more indicative of ovarian tumor than of ascites. Serum electrophoresis done immediately revealed: albumin, 34.7; α_1-globulin, 6.1; α_2-globulin, 18.4; β-globulin, 10.2; γ-globulin, 30.6. The ratio of α_2- to β-globulin was 1.80. The finding is more suggestive of some concealed malignancy than of liver cirrhosis. Therefore, liver function tests were repeated and proved to be normal this time. On November 4, exploratory laparotomy was performed. Opening of the abdomen revealed a huge smooth-surfaced ovarian cyst and no ascites. The tumor showed adhesion only in the pelvic floor and was otherwise intact. The liver was smooth. Although the gross appearance of the tumor indicated a common pseudomucinous cystadenoma, pathologic examination disclosed a small area of cystadenocarcinoma in the ovarian cyst. After postoperative irradiation, she is doing well.

Case 2. Patient R. S. E., aged 30, underwent x-ray study and radium irradiation for uterine cancer 5 years ago. She presented herself on June 11, 1958, because of high fever and lower abdominal tumor the size of a child's head. The Papanicolaou smear test showed negative. Because of the atrophic small cervix, dilatation of the cervix in an attempt to prove pyometra was done but was not successful. Tuboovarian abscess could not be ruled out. Serum electrophoresis showed albumin, 37.4; α_1-globulin, 8.7; α_2-globulin, 17.4; β-globulin, 14.8; γ-globulin, 21.7. The ratio of α_2- to β-globulin was 1.8. Laparotomy performed at a missionary hospital in this city revealed epidermoid cancer in the uterine body with marked extension to the peritoneum. She died immediately after the operation.

Comment

Although many investigators found albumin decreases in malignant diseases, some

Table VI. Mortality rate of gynecologic malignancy patients classified by normal and abnormal ratios of α_2- to β-globulin

	$\alpha_2/\beta \geqq 1.0$		$\alpha_2/\beta < 1.0$	
Stage	*No. of cases*	*Dead or hopeless*	*No. of cases*	*Dead or hopeless*
Uterine cancer				
In situ			4	1
Stage I	2		28	
Stage II	10		35	2
Stage III	20	13	11	2
Stage IV	4	4	2	
Recurrent malignancies	9	9		
Gynecologic malignancies exclusive of uterine cancer				
Group A*			6	
Group B†	7	7	1	
Total	52	33	87	5

*Group A were cases where the lesion was localized in the primary organ.

†Group B were cases where the lesion extended beyond the primary organ.

Table VII. Mortality rate of gynecologic malignancy patients at various periods after treatment

Periods	$\alpha_2/\beta \geqq 1.0$			$\alpha_2/\beta < 1.0$			Statistical significance
	No. of cases	Dead (dead or hopeless)		No. of Case	Dead (dead or hopeless)		
		Case	%		Case	%	
12-14 months	15	11	73.3	33	3	9.1	26.70
6-12 months	23	11	48.8	41	1	2.4	19.923
		(14)	(60.9)		(2)	(4.8)	(24.64)
2-6 months	14	4	28.6	13	0	0.0	4.352
		(8)	(57.3)				(10.56)
Total	52	26	50.0	87	4	4.6	41.200
		(33)	(63.4)		(5)	(5.7)	(54.58)

believe hypoalbuminemia is not characteristic of malignant disease.[24] The cause of hypoalbuminemia has been explained by the imbalance between synthesis and destruction of serum protein or by the inflammation and bleeding complicated by cancer. We found the decrease of albumin proportional to the progress of cancer but irreversible even after the cancer was cured. As Seibert[20] has emphasized, and as was found in our series, a slight but significant increase of γ-globulin was noted, which was in proportion to the advance of cancer but irreversible even after healing of the cancer. In our series, α_1- and α_2-globulin, particularly the latter, show a marked increase in advanced uterine cancer and definite decrease with the retrogression of the disease. β-globulin shows, on the contrary, a decrease in advanced uterine cancer and a definite increase with the retrogression of the disease. The increase of α_2-globulin in cancer cases has been reported by many investigators[10, 13, 18-21] and Greenspan[9] has emphasized the significance of mucoprotein of α-globulin in the differential diagnosis of malignant and nonmalignant liver diseases. It is noteworthy that recently Gilbert and his associates[7] have reported the same pattern of serum electrophoresis as ours in leukemia cases. It awaits further investigation whether the change of α-globulin is of a specific nature in malignant diseases, or of a nonspecific nature, due only to tissue destruction, fever, or infection.

On the basis of the foregoing results of our experiments, we are rather inclined to lay stress on the abnormal ratio of α_2- to β-globulin as a characteristic of advanced malignancies, which will find further corroboration in any clinical findings suggestive of malignant lesions. As Table VI indicates, only a few cases of Stage I and II uterine cancer show such a pattern of electrophoresis. Therefore, the value of the ratio in early diagnosis is very limited, while in advanced, deepseated, concealed malignant lesions, the abnormal ratio gives very valuable diagnostic support. As the follow-up observation indicates (Tables VI and VII), the abnormal ratio foretells a poor prognosis. Our clinical experience indicates that the return from the abnormal to the normal ratio after treatment reflects an excellent therapeutic response of the disease, although whether or not it promises a good prognosis merits further investigation. On the contrary, a persisting abnormal ratio after treatment foretells a bad outcome. A shift of the ratio from the normal to the abnormal pattern means steady progress or recurrence of cancer, therefore, also indicating a bad prognosis.

Summary

In the studies of serum protein in uterine cancer cases using paper electrophoresis, the following conclusions were drawn:

1. The decrease of albumin and increase of γ-globulin resulting from uterine cancer are irreversible even after the cure.

2. The increase of α_1- and α_2-globulin and decrease of β-globulin are constant findings in advanced uterine cancer.

3. In normal patients and a majority of those with early uterine cancer the ratio of α_2- to β-globulin is below 1.0.

4. In a great majority of advanced uterine cancer cases, the ratio of α_2- to β-globulin is above 1.0.

5. The ratio of α_2- to β-globulin above 1.0 (the abnormal ratio) can be used as a supplementary diagnostic tool for advanced pelvic malignancies, particularly, concealed, deep-seated lesions.

6. The ratio of α_2- to β-globulin above 1.0, particularly when it persists after treatment, indicates a bad prognosis.

7. A shift of the ratio of α_2- to β-globulin from the normal to the abnormal pattern means steady progress or recurrence of cancer, also indicating a bad prognosis.

8. The change of the ratio of α_2- to β-globulin can be used as an indicator of the response of uterine cancer to treatment.

9. In early cases of uterine cancer, the deviation of serum protein is so slight that it is hardly usable in early diagnosis, evaluation of therapeutic response, or prognostication of the disease.

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Carcinoma in situ of the cervix in a monkey (Macaca mulatta)

Report of a case

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AN EXPERIMENTAL monkey used in a toxicity test[1] with a potential cancer chemotherapeutic agent was found at autopsy to have an in situ carcinoma of the cervix. It is believed that this tumor represents the first of its type to be reported in a simian primate.

The animal was a *Macaca mulatta* of unknown age purchased from a local animal dealer who had recently received it in a shipment from India. After arrival in the laboratory it was skin tested with old tuberculin and found to be free of active disease. At the beginning of the experiment, the animal was in good health and weighed 4.51 kilograms. The test material, an antibiotic* obtained from strains of *Streptomyces flocculus,* was injected in repeated daily intravenous doses. The animal died 4 days after receiving 4 successive doses of 25 γ per kilogram per day. On the day of death the animal was depressed and offered no resistance when removed from the cage. The weight at this time was 4.37 kilograms.

Autopsy was performed 30 minutes after death. Gross examination revealed numerous hemorrhages in the epicardium and myocardium of the ventricles. The lungs contained multiple gray nodules measuring up to 0.7 cm. in diameter. The right kidney contained several thin-walled cysts in the lower pole. Both renal cortices were thickened and pale. No other noteworthy gross alterations were present.

Initially, a single random section from the cervix was taken for microscopic examination. This contained an area of in situ carcinoma near the junction of the squamous epithelium of the vagina with the endocervix (Fig. 1). (In the human, this would correspond to external os.) In this region there was an abrupt change in the character of the normal squamous epithelium marked by a loss of polarity of the epithelial nuclei. The individual cells were irregularly enlarged and hyperchromatic; there was an increased nuclear-cytoplasmic ratio and the nuclear chromatic arrangement was abnormal. The process continued into the adjacent endocervical epithelium and into several underlying glands (Fig. 2). Subsequently, the remaining cervix was totally embedded and sectioned. Several smaller foci of carcinoma were detected in the endocervical epithelium (Figs. 3 and 4). Infiltration of the stroma was not present in any of the sections. In addition, there were several areas of simple squamous metaplasia in the endocervical tissue. The only other abnormality noted in the cervix and vagina was the presence of moderate numbers of lymphocytes in the subepithelial tissues. In one portion of the vagina these inflammatory cells formed a small lymphoid follicle. This process was considered to be moderately severe nonspecific cervicitis and vaginitis.

The ovaries contained numerous ova and

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**Streptonigrin,[2, 3] supplied by the John L. Smith Memorial for Cancer Research, Chas. Pfizer & Co., Inc., Maywood, New Jersey.*

atretic follicles. The endometrium was in the proliferative phase. Several small hemorrhages were present in the endometrial stroma. The myometrium and Fallopian tubes were normal. Numerous hemorrhages of recent origin were present in the myocardium. The lung nodules represented infestation by mites (pulmonary acariasis). A membranous glomerulonephritis was present in the kidneys; in addition, there were several necrotic proximal convoluted tubules. One kidney contained several simple cysts lined by flattened epithelium.

The following tissues were also examined microscopically and showed no abnormalities: buccal mucosa, tongue, tonsil, submaxillary salivary gland, lymph node, thyroid, thymus, liver, gall bladder, spleen, pancreas, adrenal gland, stomach, duodenum, colon, ureter, bladder, vertebral and sternal bone marrow, and spinal cord.

Comment

It is most unlikely that the antibiotic was responsible in any way for the development of the tumor in view of the short duration of exposure (4 days) to the substance. Furthermore, there were no alterations in the tumor cells that would indicate that the antibiotic had affected them in any way. The animal died from toxicity to the test material, and this was reflected primarily in the extensive hemorrhages in the heart. The glomerulonephritis may also have been related to toxicity.

The cancer in this monkey is morphologically similar to in situ carcinoma of the cervix in the human. The following features of the monkey lesion bear out this comparison: (1) the principal alteration occurred in the vicinity of the squamocolumnar junction, where an abrupt change was seen between the benign squamous epithelium and the carcinomatous area; (2) the cytologic alterations were those found in carcinoma in situ in the human (loss of cellular polarity, increased nuclear-cytoplasmic ratio, chromatin particles of abnormal size and arrangement), and (3) the process extended into the endocervical glands.

Although the actual age of the monkey was not known, the animal was judged to

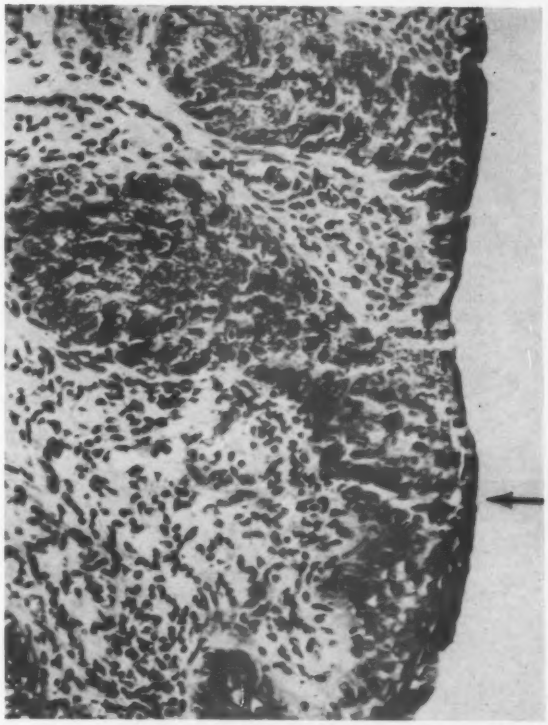

Fig. 1. In situ carcinoma in continuity with benign squamous epithelium. Arrow indicates junction of the two zones (artifactually divided by a slit).

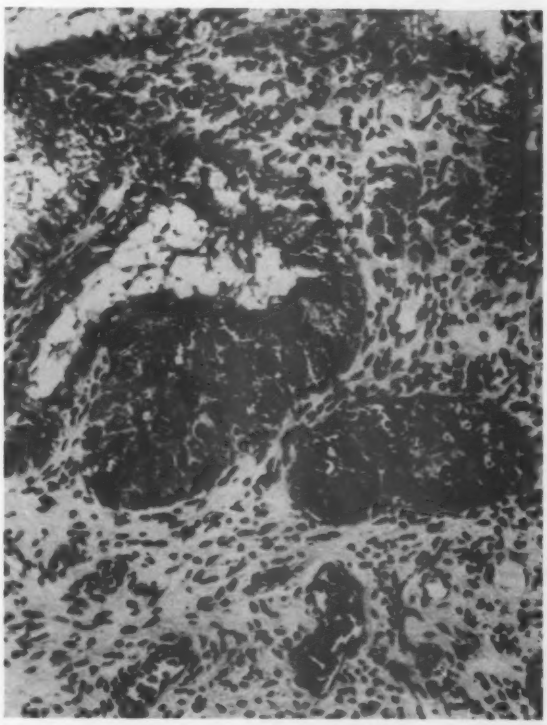

Fig. 2. Carcinoma extending into glands underlying surface epithelium illustrated in Fig. 1.

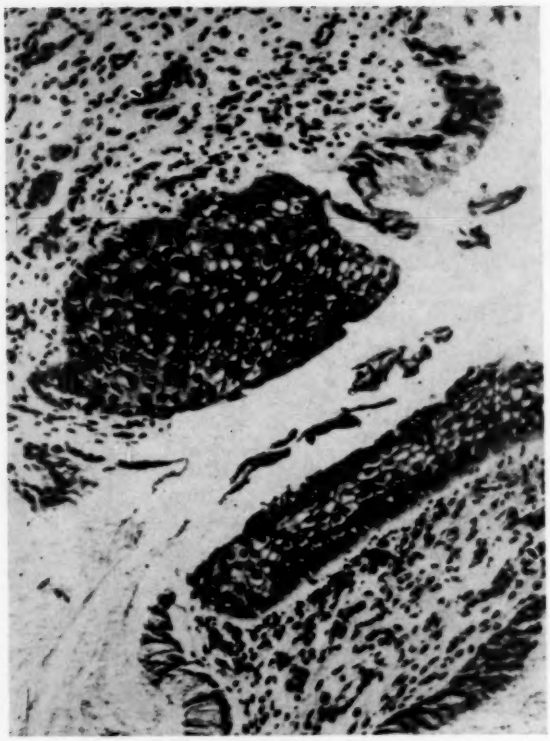

Fig. 3. Metaplastic areas showing in situ carcinoma in upper and marked atypia in lower focus.

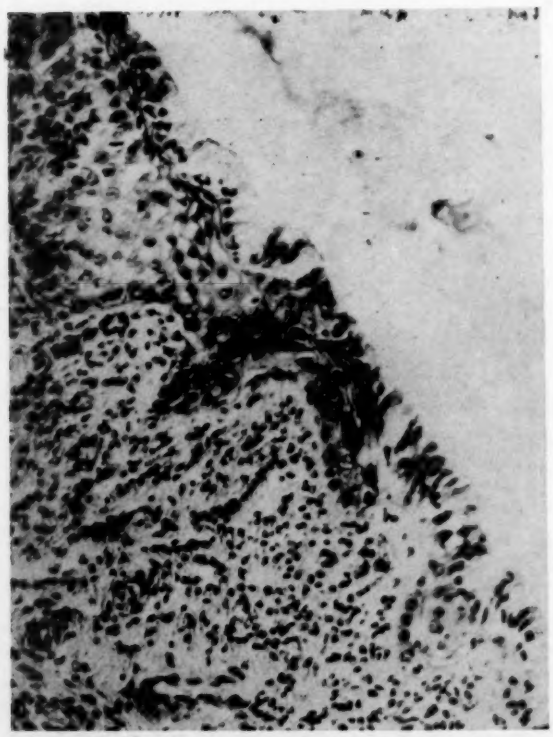

Fig. 4. Another focus of in situ carcinoma. Note enlarged and hyperchromatic nuclei. Above this focus and in continuity with it the metaplasia is benign and typical.

be a young adult. This was based on the appearance of the ovaries and endometrium which indicated that the animal was sexually mature. On the basis of weight alone the age was estimated to be between 5 and 6 years.[4]

The recent report by Hisaw and Hisaw[5] of a metastasizing carcinoma of the cervix in an old *Macaca mulatta* was the first documented case of that type in the monkey. The tumor in this case was considered by them to be similar to the human variety; the local infiltration and metastases corresponded to Stage IV in the League of Nations classification. Despite the apparent rarity of this type of cancer in simian primates they felt that further examples of the disease should be looked for in these species. The present example of the same type of cancer, in a noninfiltrating stage, and in an animal younger than theirs, represents additional support for their suggestion.

It seems reasonable to suggest that monkeys in laboratory colonies and in zoos be periodically examined by the Papanicolaou cytologic technique in the hope of discovering additional cancers of this type. The monkey represents the only laboratory animal known to develop spontaneous cervical cancer of a type which is similar to the human variety. Perhaps with such a laboratory animal, environmental and other factors such as religion, circumcision, smegma, virginity, and parity (which have been implicated in one way or another in human cervical cancer) could be more objectively examined as variables in the development of this disease.

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Diagnostic significance of ciliated cells in human endometrial tissue cultures

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CILIATED cells are a rather common constituent of an endometrial tissue culture. During a 6 year study on the behavior and the potentialities for differentiation and growth of normal, benign, and malignant human endometrial cells, their presence was noted in 86 out of a total of 575 cases. Information regarding the techniques used and the source of the material can be found in previous publications.[1-3]

A brief account of our observations on ciliated cells, as given in these earlier papers is as follows: "Ciliated cells were observed in a fair number of living cultures. Their ciliary movement could be distinctly seen in some instances for as long as 5 to 10 days. Many ciliated cells were detached while others formed a continuous border on the surface of the explant. In fixed and stained cultures, ciliated cells were only rarely observed, probably because they were lost in the course of these procedures. It is perhaps for this same reason that ciliated cells could not always be demonstrated in sections of endometrial tissue obtained during the operation. In some instances, however, a correlation between living and fixed cultures on one hand and tissue sections on the other has been possible. In the majority of the cases in which ciliated cells were noted, the diagnosis was that of a benign endometrial polyp or polypoid hyperplasia. The best endometrial explant with a well-preserved ciliated border observed in our series in a fixed and stained 48 hour culture was in the case of an endometrial polyp. In general, explants from polypoid tissue exhibited a relatively high growth potential."

A more detailed description of our observations is given in the present paper. A statistical analysis of the 86 cases, in tissue cultures of which ciliated cells were observed, shows that hyperplasia of the endometrium or an endometrial polyp was diagnosed pathologically in 44 cases (51.16 per cent) and clinically in 18 (20.93 per cent), i.e., in a total of 62 cases (72.09 per cent). In the remaining 24 cases (27.91 per cent) there has been no operative or clinical evidence of either hyperplasia or a polyp. Since no surgical exploration was performed in these 24 cases, the negative diagnosis should not, of course, be considered as conclusive. Of the 62 pathologically or clinically positive cases 25 were diagnosed as endometrial hyperplasia, 24 as endometrial polyp, and 13 as polypoid hyperplasia.

The above figures indicate that the presence of ciliated cells in a tissue culture is strongly suggestive of endometrial hyperplasia or a polyp. Endometrial tissue fragments with a ciliated border have also been occasionally seen in some of the relatively few cases in which endometrial aspiration

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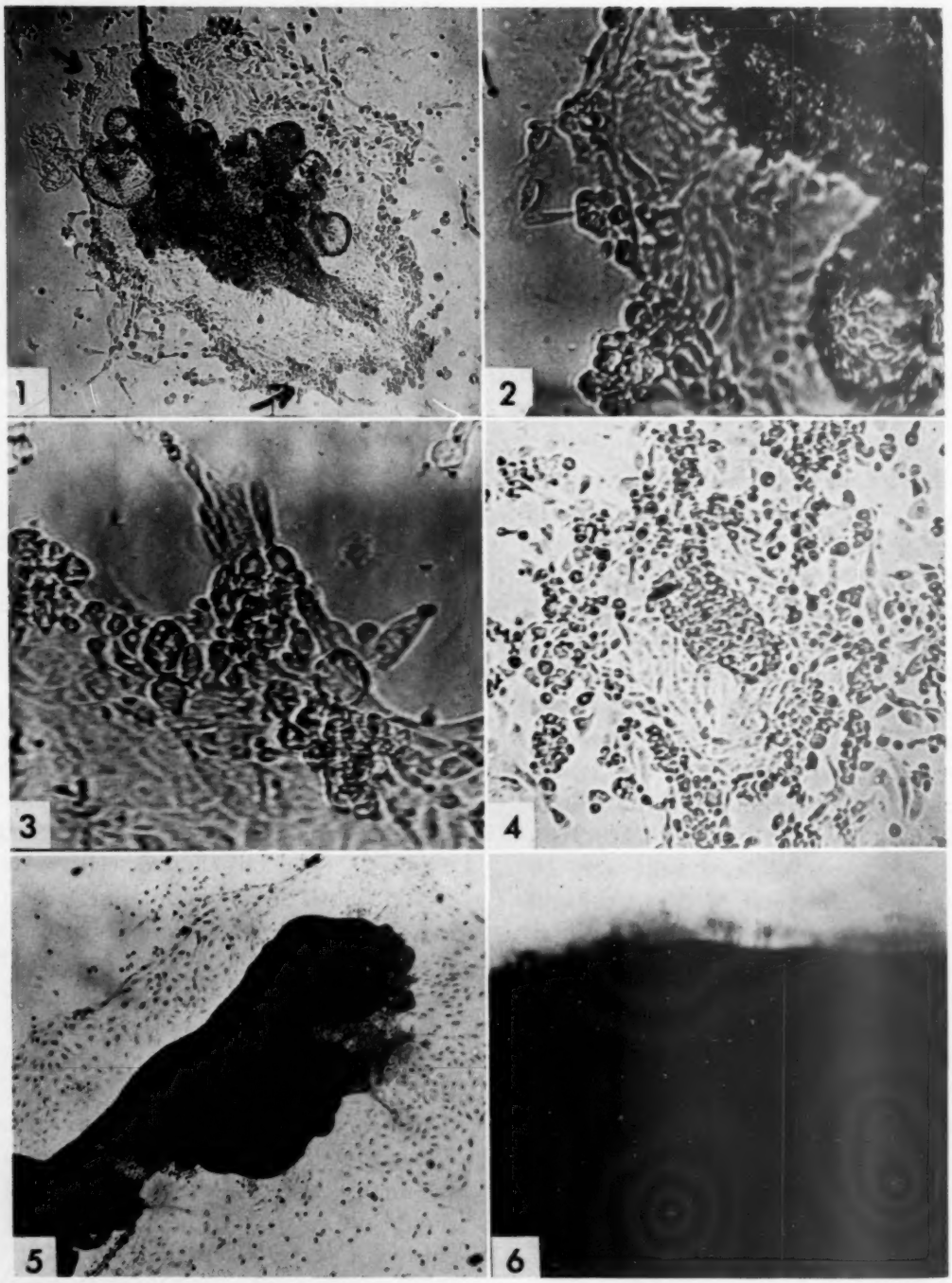

Fig. 1. Five-day living tissue culture of endometrial aspiration demonstrating active outgrowth of cells from an endometrial explant. (×50.)

Fig. 2. Higher magnification from upper area of Fig. 1 indicated by arrow. (×250.)

Fig. 3. Higher magnification from lower area of Fig. 1 indicated by arrow. (×250.)

Fig. 4. Five-day living tissue culture from same case. (×100.)

Fig. 5. Fixed and stained 7 day tissue culture from same case demonstrating outgrowth of cells from an endometrial explant with ciliated border. (×50.)

Fig. 6. Same as Fig. 5, showing an area of the ciliated border under higher magnification. (×1,200.)

smears were taken at the time the tissue culture material was obtained. The apparent scarcity of ciliated cells in fixed and stained tissue cultures may be largely attributed to the fact that many ciliated cells lose their cilia during fixation and staining, thus making their identification very difficult. This is why one has to rely chiefly on the living tissue culture for demonstrating the presence of ciliated cells.

Both the Maximow and the roller tube techniques were used in this study. Both techniques appear to be suitable and both are recommended, although the Maximow culture holds a certain advantage with regard to the evaluation of the growth pattern and the structural characteristics of the cells of an explant. If only roller tube cultures are used, it is suggested that before culturing the tissue and cells be viewed microscopically under the most sterile conditions possible, in order to ascertain whether there are ciliated cells or borders present. This is advisable since the roller tube does not lend itself well to such an examination. In a Maximow culture one is able to observe the ciliated cells and borders immediately after implantation. By placing an endometrial aspiration in Ringer's solution and examining it under the microscope one may be able to verify even more quickly the presence of ciliated cells or borders in a given specimen.

Ciliated cells have been noted in an active state in tissue cultures for several days up to a maximum of about 10 days. At times cells may become detached from the ciliated border and migrate away from the explant.

In general, polypoid tissue exhibits in tissue culture very active growth comparable to that of the normal proliferative stage or of a malignant neoplastic growth.[2] Cellular growth may appear as early as 16 to 24 hours after the setup of the culture.

Summary

1. Ciliated cells found in a relatively high percentage of cultures of endometrial tissue or aspirated fluid obtained from cases diagnosed pathologically or clinically as hyperplasia or polypoid growth appear to be significant and, therefore, are of definite diagnostic value.

2. Ciliated cells can be best demonstrated in the living tissue culture since their identification in fixed and stained cultures is very difficult because of the extensive loss of their ciliated border.

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Blood flow in the myometrium and endometrium of the uterus

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SINCE the fundamental experiments of Bartelmez,[2] Markee,[16, 17] and Reynolds,[24] gynecologists have made great efforts to find a useful method of measuring the blood flow in human uteri. Assali[1] described a method of catheterization and cannulation of the uterine veins, which he himself found to be a hazardous and delicate procedure. It is also evident that normal physiology may be changed by the anesthesia and by the trauma of catheterization.

The measurement of the blood flow by Na^{24} clearance[7] also deserves attention. These authors could not find significant changes in Na^{24} clearance during different stages of the cycle in cases of dysmenorrhea and pelvic congestion. They emphasized that this method of clearance may not permit conclusions about the blood flow of the entire uterus since the elimination of sodium from the compact cervical stroma may involve different pathways. Morris and associates,[20] however, have demonstrated a prolonged half-value time in pregnant women suffering from toxemia, which they suggest might be the result of ischemia of the uterus. These authors injected Na^{24} isotopes into the uterine wall by the transabdominal route.

According to the experiments of Kety,[13] Burton,[4] Wisham and Yalow,[27] and Walder,[26] the Na^{24} method of muscle clearance is not suitable for measuring the uterine blood flow, since the elimination of the injected substance is not proportional to the blood flow in the muscle. Other uncontrollable factors are the sodium retention by the tissues in toxemia, the uterine contractions developing as a reaction to the puncture, the precise position of the deposit in the tissue, and the local blood flow, which depends on the site of placental implantation. Prolonged observation is not possible by this method because the time of approximate measurement is limited to 30 minutes.

The first effort to measure the blood flow in the endometrium by thermoelements was made by Loeser,[15] using a modification of a stomach probe described by Richards, Wolf, and Wolff.[25] It was, however, impossible for him to obtain a quantitative correlation between recordings of the galvanometer and the blood flow. The impressive results of Duncan and Taylor[5] with regard to vaginal blood flow in connection with psychic stress cannot be applied, of course, to the uterine blood flow.

In summary, the results of the animal experiments by Markee[19] and Reynolds[24] have not heretofore been verified in human uteri because there has been no simple, harmless, and compatible test for recognition of physiologic, continued, long-term changes in blood flow. Since human uteri have anatomic, physiologic, and pharmacologic differences from dogs, cats, and rats, conclusions from

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animal experiments are not necessarily valid for human beings.

Basic principles and technique

In 1933 Gibbs[8] first described a method for determination of the blood flow in tissues by thermocouples. Grayson[9] and Hensel[10] and others[11, 12] later rendered this method more practical. The method depends on the principle that the temperature of a constantly heated thermocouple will be changed by a flowing medium in contact with it. The elimination of heat from a solid substance depends upon certain intrinsic qualities, but in living tissues there is the additional factor of heat loss due to the circulating blood flow.

The complex function of thermal conductivity *(Wärmeleitzahl)* includes factors of conduction and convection as well as the radiation of heat. It is reasonable to attribute

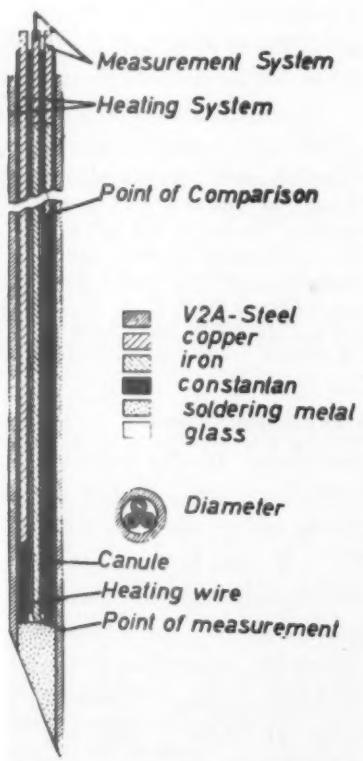

Fig. 1. Diagram of the probe used to record myometrial blood flow (external diameter 0.9 mm.; difference from point of measurement to the point of comparison 10 mm.). For further description see text. (From Prill, H. J.: Ztschr. Geburtsh. u. Gynäk. 152: 79, 1959; Ferdinand Enke, Verlag, Stuttgart.)

Fig. 2. Position of the probes for measuring the blood flow in the human uterus. *1*, Endometrial probe; *2*, tube for inflating the balloon for registering the intrauterine tonus; *3*, myometrial probe. (From Prill, H. J.: Ztschr. Geburtsh. u. Gynäk. 152: 82, 1959; Ferdinand Enke, Verlag, Stuttgart.)

a change in thermal conductivity to a change in the blood flow (convection) because radiation of heat from a point within the body may be neglected and blood conduction is only a minor factor in producing changes in thermal conductivity (Hensel and Bock).[11]

The development by Hensel and Rueff[12] of a thermal conductivity probe for the skeletal muscles furnishes us with the opportunity for continuous thermal conductivity measurements in the myometrium, which permits a relative comparison with the blood flow. Linzell[14] and Hensel and Rueff[12] made model experiments with artificially perfused media, from which they could show a linear function, within physiologic limits, between increasing values for the blood flow and the figures for thermal conductivity.

A constant quantitative relationship between a moderate blood flow conductivity, as Grayson[9] supposed, could not be confirmed by Hensel.[11] In positions particularly near blood vessels with a high blood flow rate, deviations arise which will be measured as deceptively minimal variations. For this reason, as will be discussed later in this paper, compression of the aorta was resorted to in order to obtain more accurate values for changes in blood flow.

The probe for the myometrium is a 60

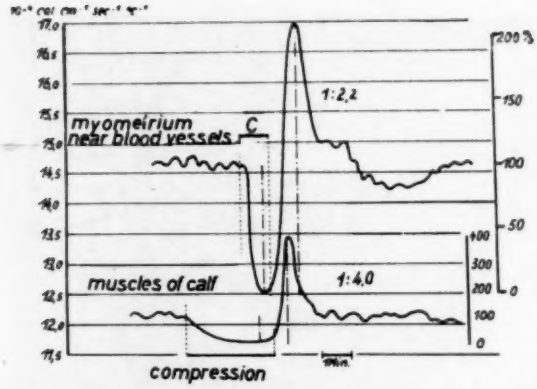

Fig. 3. Effect of aortic compression (= C) on the myometrial blood flow compared with the effect of compression of a leg cuff on the blood flow of the calf. (Scale on the left side = thermal conductivity [λ]; scale on the right side = percentual evaluation of the blood flow; $\left.\begin{matrix}1{:}2.2\\1{:}4.0\end{matrix}\right\}$ = compression : reactivity hyperemia.) (From Prill, H. J.: Ztschr. Geburtsh. u. Gynäk. 152: 89, 1959; Ferdinand Enke, Verlag, Stuttgart.)

mm. long cannula with an external diameter of 0.9 mm., i.e., similar to a needle for intramuscular injections (Fig. 1). For the uterine cavity a flexible probe is used for better adaptation to the endometrium (Fig. 2). At the closed apex of the cannula and in the end of the probe is installed a heating circuit which is charged with a constant alternating current of 0.2 to 0.6 amperes. A second circuit for measuring the difference of temperature is inserted within probe and cannula, about 10 mm. from the apex, but connected with it by a metallic contact. The heated apex of the probe, maintained at constant temperature within 3° C. above the local body temperature, represents the warmed medium; its temperature changes with the blood flow. The figure for thermal conductivity is obtained from the measurement of the difference of the temperatures recorded in the two circuits, the heating current being constant.* The results are calculated from the formula: λ (figure of thermal conductivity) =

$$\frac{k\ (\text{constant factor}) \times I^2}{\delta\ (\text{difference of temperatures})},$$ where I = intensity of heating current.

*The complete measuring circuit is now obtainable as the "Fluvograph." Producer, Hartmann & Braun, Graeffstrasse, Frankfurt am Main.

Further description of details is not necessary because they have been fully described elsewhere[9-12, 22, 23] (Fig. 2).

The probe must be buried at a point 3 to 4 cm. above the external os near the isthmus of the uterus because this area appears to exhibit the best relation between measured conductivity and blood flow. The endometrial probe is inserted through the internal os of the uterus within a catheter and then advanced into the uterine cavity (Fig. 2). This flexible probe has the same principle as the myometrial probe. To maintain a constant position of the probe, it is advisable also to attach a small rubber balloon, filled with water or air, for registering the oscillations of the intrauterine pressure, because these oscillations may cause a variation in the blood flow.

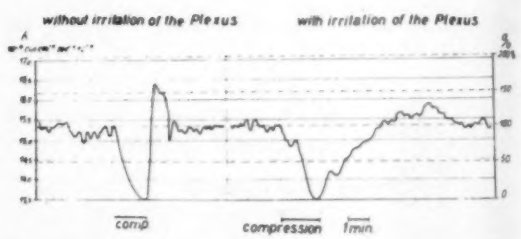

Fig. 4. Effect of aortic compression on the myometrial blood flow without and with irritation of the solar plexus. (Scale on the left side = thermal conductivity [λ]; scale on the right side = percentual evaluation of the blood flow; comp. = compression.) (From Prill, H. J.: Ztschr. Geburtsh. u. Gynäk. 152: 90, 1959; Ferdinand Enke, Verlag, Stuttgart.)

Myometrial blood flow

The knowledge of the values of thermal conductivity in a dead organ without any circulation is prerequisite to measuring the blood flow of the human uterus. Eleven normal and 8 pathologic uteri were examined for determination of the thermal conductivity. Grossly normal-appearing tissue showed a fairly constant figure for thermal conductivity: $11.7 \cdot 10^{-4} \cdot$ cal. $\cdot$ cm.$^{-1} \cdot$ sec.$^{-1} \cdot$ °C^{-1}* ($\sigma \pm 0.36$).

The thermal conductivity in specimens of older persons may be somewhat lower than

*In subsequent figures for thermalconductivity the factors $10^{-4} \cdot$ cal. $\cdot$ cm.$^{-1} \cdot$ sec.$^{-1} \cdot$ °C^{-1} will be omitted.

that of younger persons, probably because of an increase in fibrous tissue or decrease in fluid content. In some cases also myomatous tissue was found to have a higher thermal conductivity. According to Grayson[9] the thermal conductivity of dead tissue depends to a great extent upon the fluid content, which in myomatous tissue may vary with softening or calcification. The myometrium in late pregnancy and also in early carcinoma did not show any significant variations. The endometrium yielded a constant figure ($\lambda = 11.2$, $\sigma = \pm 0.22$) regardless of the phase of the cycle. In summary, it was found that the thermal conductivity of dead myometrium and endometrium is uniform and the figures thus obtained provide baseline values for measuring blood flow.

Blood flow measurements in 71 patients have been obtained. The blood flow during rest in approximately 50 per cent of all tests was found to be between $\lambda = 15$ to 16, although with the instrument in positions near blood vessels a rise to $\lambda = 20$ is sometimes noted. Thermal conductivity in the myometrium may be recorded below $\lambda = 14$, and in such cases a change in the position of the probe is advisable. Since resting skeletal muscles have a thermal conductivity of only $\lambda = 12.2$, *the blood flow rate in the myometrium is significantly higher* ($\Delta\lambda = 3.5$). The examined group is summarized according to age and diagnosis in Table I.

Table I. Measurements of blood flow in the myometrium

	No. of cases	*Resting blood flow*	σ
Diagnosis			
Normal women	30	15.8	±0.94
Abortions	15	16.4	1.29
Myomatous uteri	7	15.1	1.29
Tumors of the ovaries and pelvic inflammatory diseases	8	16.0	0.84
Age (years)			
18-30	18	16.1	1.25
31-40	13	15.4	0.87
41-50	17	15.1	0.85
51-60	5	14.7	0.83

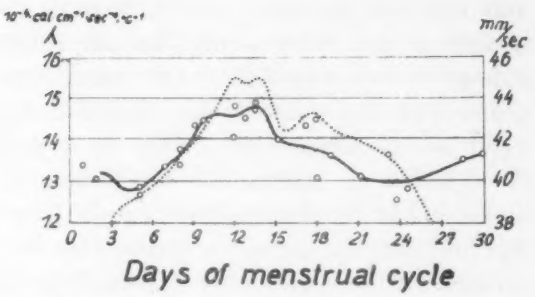

Fig. 5. Results of blood flow measurement on the endometrium during the cycle. Dotted line = average values of blood flow measurement on transplanted endometrium in monkey's eyes by Markee.[18] Measuring system (mm./sec.) on the right side of the figure (black line) = average values of thermal conductivity (λ) on the human endometrium. Measuring system on the left side. (From Prill, H. J.: Ztschr. Geburtsh. u. Gynäk. 152: 95, 1959; Ferdinand Enke, Verlag, Stuttgart.)

The average thermal conductivity among the sexually healthy women was found to be $\lambda = 15.8$. In cases of abortion, somewhat higher blood flow rates ($\lambda = 16.4$) were observed. In cases with fibrous uteri the figure was lower ($\lambda = 15.1$), perhaps as a result of poor blood flow in the fibrous areas.

With increasing age the diminution in average blood flow is significant. The difference is quite apparent when comparing the 18 to 30 and 51 to 60 age groups, this corroborating the observations made by Flick, Shettles, and Taylor[7] with isotopes. Variations in circulation of the myometrium with respect to the menstrual cycle have not been established after comparative measurements among several persons tested. This is surprising in view of the cyclic changes of the blood flow in the endometrium.

A difference of $\Delta\lambda = 4$ between the dead myometrium, i.e., without circulation, and similar tissue with intact circulation provides a basic ratio in which one sets the average value of the uncirculated tissue at 0 and the resting blood flow at 100.

Effects of compression of the aorta

A functional test provides a better quantitative evaluation of the change of circulation. This test consists of alternately compressing

and releasing the aorta at the level of the umbilicus and determining the percentage change in local blood flow. Of course, compression of the aorta by the hand is not as exact as compression of a limb by a cuff. Nevertheless, a comparable blood flow reaction could be demonstrated in the lower legs following the use of the cuff and by compression of the aorta. Decompression of the aorta is followed by a reactive hyperemia in the blocked circulated area. This reactive hyperemia, however, shows a somewhat different pattern in the skeletal muscles (Fig. 3).

The average value of all "compression curves" was $\lambda = 13.4$. Consequently a diminution of thermal conductivity of about $\Delta\lambda = 2.4$ was obtained by the procedure of compression. This value, three times that obtained in the skeletal muscles, supports our assumption of a higher blood flow rate in the myometrium. Nevertheless, reduction to the level of uncirculated tissue could not be obtained. In our opinion the cause is the imperfect manual technique, the necessary shortness of compression, and also the anatomic situation, especially the high origin of the ovarian and renal arteries. Aortic compression is suitable for percentage determination of an increase or decrease in the blood flow since the effect of compression proved to be constant ($\sigma = \pm 0.9$). Compression of the aorta was not satisfactory in women with tight abdominal walls and obesity (17 per cent of all cases). Broad compression of the aorta sometimes affected the solar plexus and celiac ganglion lying near the aorta, resulting in delayed resumption of the resting blood flow, and was eventually followed by hyperemia of 3 to 5 minutes' duration (Fig. 4). This different blood flow reaction probably has its explanation in the pressure on the nervous plexus as recently demonstrated by von Euler and Folkow.[6] The ensuing hyperemia is slight in amount and brief in duration ($\Delta\lambda m = 0.6$). A greater increase in blood flow ($\Delta\lambda = 2$-3) can be demonstrated frequently when the probe is located near blood vessels (Fig. 3).

Blood flow in the endometrium

The measurement of the circulation was carried out on the endometrium of 36 women. A figure of thermal conductivity of $\lambda = 11.2$ ($\sigma = \pm 0.22$) was determined on specimens of the endometrium with absent circulation and was found to be independent of the cyclic phase. The mean value for the endometrium with intact circulation was $\lambda = 13.7$ among 26 women with normal cycles. This mean value is $\Delta\lambda = 2.5$ smaller than for myometrium but $\Delta\lambda = 1.5$ higher than for skeletal muscles. The lesser circulation, as compared to myometrium, may be due to the smaller diameters of the blood vessels. The higher value as compared with the skeletal muscles is perhaps due to the extensive capillary endometrial network.

The endometrial blood flow showed certain curves according to the day of the cycle. The little circles in Fig. 5 represent the results of individual measurements, the black line the mean values. The results were compared with those obtained by Markee[18, 19] in studying the circulation of transplanted endometrium in monkey's eyes. Inasmuch as he had used an entirely different system, the conformity of the two curves is amazing. *An increase in blood flow was found up to the middle of the cycle, followed by a gradual decrease.* We believe we were able, therefore to confirm Markee's animal tests in human endometrium (Fig. 5).

The effect of aortic compression could also be shown in the endometrium. This effect is less than in the myometrium, in consequence of the smaller thermal conductivity and the slower decrease in blood flow during the aortic compression observable in the endometrium. The reactive hyperemia was also found to be lower or undetectable in the endometrium.

Results reported elsewhere

Our results of blood circulation measurement in the uterus during labor and under different hormonal and pharmacological influences are reported elsewhere.[21-23] Some results may be briefly mentioned:

1. During abortions in the third and

fourth months a single contraction will lower the blood flow about 40 to 70 per cent.

2. Epinephrine (8 to 25 γ intravenously), diminishes the blood circulation about 30 to 70 per cent. The effect of norepinephrine (10 to 30 γ intravenously) is very small. The application of sympathicolytic drugs inhibits the effect of epinephrine in the myometrium.

3. Parasympathicomimetic and sympathicolytic drugs cause an increase of 20 to 55 per cent in the myometrium.

4. Estradiol dipropionate (5 mg. intramuscularly) caused an increase in blood flow of 30 to 100 per cent in the myometrium, 80 to 250 per cent in the endometrium.

5. The effect of progesterone (20 mg. anhydroxyprogesterone intravenously) on the blood flow of the uterus depends on the phase of the cycle. At the time of ovulation the blood flow increases by as much as 100 per cent. Prior to menstruation there is no increase, sometimes even a decrease.

Comment

A harmless method for the simple continuous measurement of uterine blood flow seems available to us for the first time with use of the described thermocouple. Although it is possible to obtain only a relative measurement for the myometrium, the application of the functional test of manual aortic compression affords opportunity for evaluation of blood flow change.

The higher rate of blood circulation in the myometrium compared to the skeletal muscles was unexpected, in view of the fact that the myometrium of a nonpregnant woman possesses no essential function and the metabolism might appear to be less than that of skeletal muscles. Different explanations may be offered. For the growth of the endometrium a high metabolism may be necessary. Furthermore, only a single artery is present on each side of the uterus for the supply of the large vascular network, so that a rapid flow is perhaps required.

The observation of a premenstrual decrease in the blood flow in the endometrium appears at first unbelievable to gynecologists in view of clinical observations of premenstrual hyperemia. According to our investigations this premenstrual lividity depends not upon an increased blood flow (convection) but on an increased local volume (conduction). The term "premenstrual stasis" would therefore seem appropriate.

The results of the aortic compression reaction furnish interesting points for speculation. Inasmuch as one can obtain a rapid or delayed return to resting levels of blood flow, depending on how the pressure is applied and whether the plexuses lying around the aorta are affected, in the same test person and with the same position of the probe, a neurogenic action from the solar plexus upon the circulation of the uterus has to be considered. Since contractions of the myometrium could be excluded by simultaneous measurement of the intrauterine tonus in most of the cases, the action must be caused by the nerves to the blood vessels. This may be of significance in regard to the mechanisms of bleeding of neurogenic origin. Cyclic changes in endometrial blood flow appear to us to be very significant. Based on histologic and experimental animal tests Bartelmez[2] and Markee[19] were convinced that menstruation is caused by a hormone-dependent insufficiency in blood supply of the spiral arteries. Our physical tests showed the thermal conductivity to be distinctly lower premenstrually. This seems to confirm the thesis of Bartelmez and Markee on the human endometrium for the first time. Thus, a "vascular cycle of blood flow" has been shown in the human endometrium, with the highest blood flow at ovulation.

Summary

1. With the use of the principle of thermal conductivity measurement of Gibbs,[8] Grayson[9] and Hensel and co-workers[10-12] an appropriate method is described for measuring the blood flow of the human myometrium and endometrium.

2. As a basis for comparison the effect on local blood flow of aortic compression at the level of the umbilicus provides a suitable functional test.

3. In dead myometrium without circulation a figure of $\lambda = 11.7$ in thermal conductivity was found, in myometrium with intact circulation a value of $\lambda = 15.7$. The higher value is produced by the blood flow.

4. The blood flow of the myometrium was shown to depend upon the patient's age and the nature of the disease (Table I). The thermal conductivity of the myometrium was significantly higher than that of resting skeletal muscles.

5. With the heterogeneity of compression reactions and the ensuing hyperemia, interesting vasovegetative possibilities of interpretation were obtained.

6. The endometrium showed a lower blood flow than the myometrium. However, it was still higher than that of resting skeletal muscles.

7. Different rates of blood flow were shown at different phases of the cycle, with a maximum rate at the time of ovulation.

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Effect of norethynodrel on endometriosis

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IN 1958 Kistner[1] published a report on the use of 17α-hydroxyprogesterone caproate* and norethynodrel with 1.5 per cent ethynylestradiol-3-methyl ether,† two of the newer progestins, in 12 patients with presumed endometriosis. His results after 2 to 7 months of continuous therapy were encouraging. The rationale for this plan of conservative treatment rested mainly in the well-known observation that pregnancy often has a beneficial effect on endometriosis and that with the potent progestins now available a state of "pseudopregnancy" could be attained. He postulated that the regressions obtained were due to necrosis and atrophy in the artificially induced decidua of ectopic endometrium. In 1959 Andrews and co-workers[2] also demonstrated that necrosis and atrophy as well as leukocytic infiltration and macrophage activity does occur in the ectopic endometrium of patients treated with 17α-hydroxyprogesterone caproate for endometriosis.

Stimulated by Kistner's original work, we began a similar program of conservative therapy for endometriosis in May, 1958. Prior to this time, our conservative approach had consisted mainly in the use of androgens, and, like others, we were frequently discouraged by their masculinizing effects.

Norethynodrel was selected because of its lack of androgenic effect, its inhibitory effect on ovulation, and its desirable estrogenic content. Minimal duration of therapy was arbitrarily decided upon as 6 months.

At the onset of this study we elected to treat only patients in whom the diagnosis was made or confirmed by culdoscopy or, in a few cases, laparotomy. From a large group (1,500 cases) of culdoscopies previously reported,[3] we had learned that our preoperative diagnosis of endometriosis was correct only 54.3 per cent of the time. Furthermore, 7.3 per cent of patients suspected of having chronic pelvic inflammatory disease had unsuspected endometriosis. It was further decided that after the course of continuous norethynodrel therapy all patients would be readmitted for repeat culdoscopy and re-evaluation. By this approach we felt we would be not only accurate in our initial diagnoses but as objective as possible in our evaluation of results with progestational therapy.

In order to make this study even more objective, a special Endometriosis Clinic was established. All patients with endometriosis were seen in this clinic at monthly intervals or more often, and their disease was repeatedly evaluated by the same examiners. Following repeat culdoscopy, patients were again seen at monthly intervals for 6 months, then at less frequent intervals, depending upon their symptoms.

Study group

Between May, 1958, and May, 1960, a total of 123 patients diagnosed at Walter Reed General Hospital as having endometri-

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**Delalutin, E. R. Squibb & Sons.*

†Enovid, G. D. Searle & Company.

Table I. Symptomatology

Dysmenorrhea	80
Infertility	54
Dyspareunia	41
Menorrhagia	28
Pelvic pain	17
Metrorrhagia	15
Painful defecation	3
Hematuria	1
Rectal bleeding	1
Postcoital bleeding	1
Premenstrual tension, severe	1

osis were considered candidates for norethynodrel therapy. This included (1) all patients in whom operation either was not entertained or in whom it was thought that it might be avoided by medical management, and (2) those in whom the surgical procedure was conservative. The few patients treated by radical operation were not given this drug.

Of this group, 11, or 9 per cent, were Negroes. This is approximately the same percentage seen in our dependent clinics. The age of these patients ranged from 20 to 46 years. Average age at the time of diagnosis was 32.8 years.

Signs and symptoms

As might be expected, the most frequent complaints were dysmenorrhea and dyspareunia (80 and 41 patients, respectively). Fifty-four patients gave a history of involuntary infertility ranging from 2 to 16 years. Menorrhagia was found in 28 patients, metrorrhagia in 15, and pelvic pain not associated with menses in 17. Four patients had been treated for chronic pelvic inflammatory disease for variable lengths of time. Of the remaining symptoms, one patient with proved bladder involvement had cyclic hematuria (Table I).

Thirty-four patients had palpable endometriosis but not necessarily recognized clinically as such until culdoscopy. Of the remaining patients, the diagnosis was often entertained because of a history of dysmenorrhea and/or dyspareunia, but was not necessarily foremost in the differential diagnosis. Coincidentally, many of the latter group gave a history of involuntary infertility. In a number of instances, the diagnosis was made at the time of culdoscopy during the patient's infertility investigation.

Methods

Of the 123 patients in this study, the original diagnosis was made by culdoscopy in 111. Of the remaining 12 patients, the diagnosis was evident at laparotomy in 11 and by colpotomy in one. All patients were operated upon during the preovulatory phase and norethynodrel therapy was begun the day following diagnosis. In order to minimize nausea and vomiting the tablets were administered in gradually increasing dosages. Patients were instructed to take one-fourth tablet (2.5 mg.) daily for 4 days, then one-half tablet daily for 4 days, to be followed by one tablet daily for 2 weeks, thereafter increasing the dosage by one tablet, or 10 mg., every 2 weeks until the dose reached 30 mg. daily. If breakthrough bleeding occurred in this amount, the dosage was increased in 10 mg. increments up to a maximum of 100 mg. if necessary. During the initial phase of the study, smaller maintenance doses were administered because of our lack of experience with norethynodrel and our understandable caution. Patients were encouraged to take each day's total amount at bedtime with a glass of milk. The average necessary dose for the entire group was 49.2 mg., and 3 patients

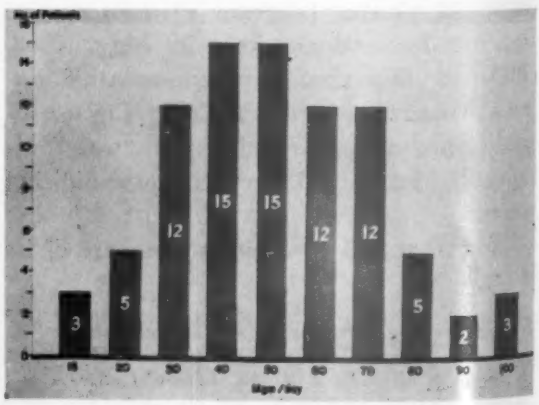

Fig. 1. Maintenance dosage of norethynodrel reached prior to initial re-evaluation.

were taking the maximum dose at the time of their readmission (Fig. 1).

All patients were seen in the Endometriosis Clinic 6 weeks postoperatively, then every 4 weeks, or more frequently, if necessary. At the time of each visit notations were made of the patients' symptoms and tolerance of the therapy. Weight was recorded and cytological smears obtained from the cervix and posterior vaginal fornix, the latter for hormonal evaluation. The pelvic findings were carefully recorded, including the appearance of the vagina and cervix, uterine size, consistency and mobility, adnexal tenderness or masses, cul-de-sac and uterosacral nodularity, and tenderness or fixation of the cul-de-sac. At the completion of therapy, in most instances 6 months, all patients were readmitted for culdoscopy, dilatation and curettage, and re-evaluation. Treatment was continued in selected patients in whom active endometriosis was still present. Regardless of the findings, all patients were referred back to the Endometriosis Clinic for monthly follow-up.

Location and extent of endometriosis

At the time of culdoscopy, the exact location of pelvic endometriosis was noted on a special culdoscopy IBM form.[3] As might be expected, the ovaries were most frequently involved. The next most common sites were the uterosacral and broad ligaments (Table II).

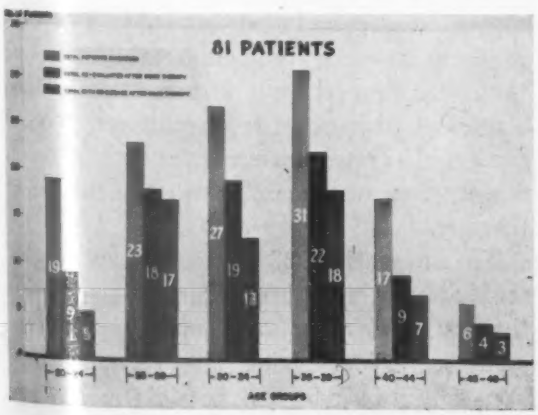

Fig. 2. Results of therapy according to age groups.

Table II. Sites of endometriosis

Ovaries		142
Right	73	
Left	69	
Large bowel		17
Uterus		16
Tubes		8
Right	4	
Left	4	
Small bowel		2
Bladder		1
Uterosacral ligaments		102
Right	49	
Left	53	
Broad ligaments		63
Right	32	
Left	31	
Infundibulopelvic ligaments		19
Right	10	
Left	9	
Pelvic walls		23
Right	9	
Left	14	

In order to better assess the effect of therapy, we adopted a simple method of classifying extent of disease. This was arbitrarily based upon the number of pelvic structures involved, paired organs being considered separately, as well as each pelvic wall and the cul-de-sac. The disease was listed as minimal if one, two, or three structures were involved, moderate if four, five, or six structures were involved, and severe if seven or more were affected.

Results

Eighty-one patients were re-evaluated by culdoscopy and/or laparotomy after 1 to 6 months (Table III). Only 4 patients (4.9 per cent) of this group were treated less than 6 months, with the average length of therapy being 5.8 months. Of this group, 51 were originally listed as having minimal disease and, of these, 44, or 86.2 per cent, had no evidence of endometriosis at re-evaluation. Twenty-four patients were originally classified as having moderate involvement and 14 of these, or 58.3 per cent, had no evidence of disease. Of 6 patients with severe endometriosis, 5, or 83.3 per cent, had negative findings. Thus, for the entire group re-evaluated after therapy, 63, or 77.7

Table III. Endometriosis after 1 to 6 months of therapy*

Type of endometriosis	*No. of organs involved*	*No endometriosis*	*Improvement*	*No improvement*
Minimal (51 patients)	1-3	44 (86.2%)	3	4
Moderate (24 patients)	4-6	14 (58.3%)	5	5
Severe (6 patients)	7-9	5 (83.3%)		1
Total (81 patients)		63 (77.7%)	8 (9.9%)	10 (12.4%)

*Only 4 patients were treated for less than 6 months; average duration of therapy was 5.8 months.

Table IV. Endometriosis after 7 to 15 months of therapy*

Type of endometriosis	*No. of organs involved*	*No endometriosis*	*Improvement*	*No improvement*
Minimal (2 patients)	1-3	1 (50%)		1
Moderate (5 patients)	4-6	1 (20%)	1	3
Severe (3 patients)	7-9	1 (33.3%)	2	
Total (10 patients)		3 (30%)	3 (30%)	4 (40%)

*Only one patient was treated for longer than 12 months; average duration of therapy was 6.3 months.

per cent, showed no evidence of endometriosis. Of the 18 remaining patients, 8 showed some improvement with treatment, 4 being in the minimal, 2 in the moderate, and 2 in the severe group. Ten patients showed no improvement—4 in the minimal, 5 in the moderate, and 1 in the severe group. We have arbitrarily placed all failed culdoscopies in the no improvement group. There was a total of 4 of these at the time of re-evaluation after 6 months of treatment.

Fig. 2 illustrates the results of therapy after 6 months, according to age groups. It is noted that regardless of age, there is little difference in the regression rate between the several groups.

Of the 18 patients who still had disease, norethynodrel therapy was continued in 8. Six of these had originally shown no improvement and after an additional 6 months of therapy, 3 had a second failed culdoscopy, one was subjected to total abdominal hysterectomy and bilateral salpingo-oophorectomy, one showed no evidence of disease, and one showed definite improvement. Therapy was continued an additional 3 months in the latter without complete regression (Table IV). The drug was discontinued in the 3 patients who had a failed culdoscopy after 12 months therapy. One has since undergone total abdominal hysterectomy and ovarian resection.

Of the remaining 10 patients who had residual endometriosis after therapy, two were treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy, while eight were allowed to resume menses.

In the total group of 123 patients, 220 culdoscopic examinations were attempted. Thirteen, or 5.9 per cent, were failures. This compares with the over-all failure rate previously reported.[3] After a course of norethynodrel, culdoscopy was successful in 2 patients after one or more previous attempts had failed.

Two patients were originally treated for a total of 8 months before repeat culdoscopy and are included in Table IV. One of these showed complete regression while the other showed some improvement. Thus, a total of 10 patients received norethynodrel for 7 to 15 consecutive months and, of these, 3 were free of disease at the conclusion of therapy.

To summarize, 83 patients were evaluated after 1 to 15 months of continuous therapy (Table V). Sixty-six showed complete regression, giving an over-all regression rate of 79.5 per cent. The average length of therapy in the entire group was 6.3 months. Only 4 patients were treated for

less than 6 months and only one for more than 12 months.

This case is presented as an example of regression of disease under treatment:

A 42-year-old gravida iii, para ii, white woman, who had had one abortion, was first seen in 1957 with a history of increasingly severe dysmenorrhea and menorrhagia. Culdoscopy was performed in December, 1957, and endometriosis was found on both ovaries and uterosacral ligaments. A 3 month course of testosterone was given, but there was no improvement. Several months later dysuria and cyclic hematuria developed, and because of this, a cystoscopy was performed. Endometriosis of the bladder wall was discovered, and treatment with norethynodrel was begun with periodic cystoscopic examinations being performed throughout therapy. There was a gradual disappearance of the endometriosis by the fourth month, and repeat culdoscopic examination revealed no evidence of disease. The drug was then discontinued and the patient has since remained asymptomatic.

Side effects

In general, the side effects of norethynodrel therapy were those commonly associated with pregnancy. The most striking and often disconcerting effect was extreme irritability and nervous tension. This was noted in 46, or 55.4 per cent, of the 83 patients objectively re-evaluated. Slightly more common but less objectional to the patients was abdominal cramping, varying in degree and often but not always associated with breakthrough bleeding. Breast tenderness was noted to some extent by 71 per cent, usually early in the course of treatment (Table VI). Other common complaints, although the exact incidence was incompletely documented, included vaginal discharge, pruritus, and leg cramps. All patients gained weight, varying from 5 to 30 pounds. In a few patients, the typical "mask of pregnancy"—darkening of the areolae, and linea nigra developed. In our experience, nausea and vomiting has not been a problem—very likely because of the dosage schedule and instructions as outlined previously. Only one patient complained of persistent nausea during treatment. All of these side effects disappeared rapidly following cessation of therapy, leaving no permanent sequelae.

Five patients required psychiatric care during norethynodrel therapy. Two of these had known psychiatric difficulties prior to therapy, one of whom eventually required institutional treatment. Acne was not noted in any patients and 7 patients had no complaints.

Seven patients of the entire study group, primarily because of side effects, refused to finish the course of treatment, discontinuing medication after periods varying from 2 weeks to 4 months. We were able to repeat culdoscopy in 2 of these, however, at a later date. Neither had residual disease and both are included in the complete regression group.

Cytological evaluation

Cervical and vaginal smears were obtained on all patients prior to therapy and at each clinic visit thereafter. Acridine orange fluorescent staining technique has been used exclusively in our clinics since 1959.[4] Smears were examined not only for evidence of cellular atypicality, but for hormonal effect and for the presence or absence of trichimonads or Candida. We have relied on the acridine orange technique for

Table V. Endometriosis after 1 to 15 months of therapy

Type of endometriosis	*No. of organs involved*	*No endometriosis*	*Improvement*	*No improvement*
Minimal (52 patients)	1-3	46 (88.4%)	3	3
Moderate (23 patients)	4-6	14 (60.8%)	4	5
Severe (8 patients)	7-9	6 (75%)	2	0
Total (83 patients)		66 (79.5%)	9 (10.8%)	8 (9.6%)

Table VI. Side effects*

Weight gain	83
Abdominal fullness	83
Breakthrough bleeding	64
Breast tenderness	59
Cramps, abdominal	51
Nervousness and irritability	46
Neuroses, requiring treatment	5
No ill effects	7

*This table includes only those patients completing 6 or more months of therapy.

documented evidence of the presence of both organisms. There was no evidence of cellular atypism prior to, during, or following norethynodrel therapy. In general, these patients showed low to moderately low estrogen effect and high to marked progesterone effect during therapy. This hormonal picture reverted to normal cyclic changes within several weeks after discontinuation of treatment. The incidence of trichimonads and Candida was less than 15 per cent. This is somewhat lower than would be expected in a similar group of pregnant women.[5]

Histological evaluation

Immediately following culdoscopy, dilatation and curettage was performed on all patients. The tissue removed after prolonged norethynodrel therapy was stringy and mucoid in appearance. Microscopic examination uniformly demonstrated a marked stromal decidual reaction with conspicuous absence and/or atrophy of glandular elements and predominance of stromal edema (Figs. 3 and 4).

Major operation following therapy

Nine patients required major operations following periods of therapy varying from 1 to 12 months. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed on 5, all of whom were symptomatic and had gross evidence of disease at the time of laparotomy. Two infertility patients underwent myomectomy at the completion of treatment. No evidence of endometriosis was found in either. One patient had an exploratory laparotomy 3 months after initiation of therapy because she was considered to have an early Stein-Leventhal syndrome. Active disease was found, although an improvement over its previous appearance at culdoscopy was noted. Polycystic ovaries were not present. The effect of norethynodrel on the ovarian stroma and ectopic endometrium is well demonstrated in Figs. 5 and 6.

The following two patients required major surgical procedures.

One patient, a 31-year-old gravida i, para i, white woman, was originally seen with a history of 11 years of secondary infertility and progressive dysmenorrhea. More recently she had noted cyclic rectal bleeding. Sigmoidoscopy was performed and endometriosis was found at 13 cm. and confirmed by biopsy. A large ovarian mass was palpated and a laparotomy was performed elsewhere. Endometriosis was found involving the uterus, left ovary, tube, and broad ligament, in addition to the rectosigmoid. Biopsy specimens were obtained, but no definitive operation was performed. The patient was transferred to Walter Reed General Hospital, and norethynodrel therapy was begun. During treatment, the left adnexal mass increased markedly in size, and after 4 months another exploratory operation was decided upon. Extensive endometriosis was found, which involved the uterus, ovaries, tubes, and rectosigmoid. A 10 to 12 cm. mass was noted on the left, incorporating rectosigmoid, ovary, and tube. A total hysterectomy, bilateral salpingo-oophorectomy, and partial sigmoid resection were performed. The postoperative course was complicated by a wound separation on the sixth postoperative day, but this was treated successfully by secondary closure. The patient has remained asymptomatic for 6 months following operation.

Fig. 7 represents the tissue removed at operation. The norethynodrel response in the ectopic endometrium is demonstrated in the sections taken from the colonic wall.

The remaining patient requiring laparotomy represents a recurrence of disease 3 months following cessation of therapy.

The second patient, a 32-year-old gravida ii, para ii, white woman, had a culdoscopy first in 1957 because of a right adnexal mass. A large endometrioma was found involving the right

ovary, and a right oophorocystectomy was performed. Endometrial implants of the left ovary and both uterosacral ligaments were fulgurized. She remained asymptomatic until August, 1958, when she noted left lower quadrant pain. Pelvic examination revealed a left adnexal mass. Culdoscopy was performed and a 6 cm. endometrioma involving the left ovary, in addition to both uterosacral ligaments, uterus, and the rectosigmoid, was found. A 6 months' course of norethynodrel was begun, during which time the mass disappeared. Following therapy, culdoscopy revealed no residual endometriosis. Three months later a 5 cm. mass was palpated in the left adnexal region. Culdoscopy was repeated, but the mass could not be well visualized. Laparotomy was performed and an endometrioma was again resected from the left ovary. No other endometriosis was noted. No further therapy was given, but 8 months later, because of metrorrhagia, she was again admitted and culdoscopy attempted, primarily for investigative purposes, but this was unsuccessful. A dilatation and curettage was performed. No further treatment was given. The patient has remained asymptomatic.

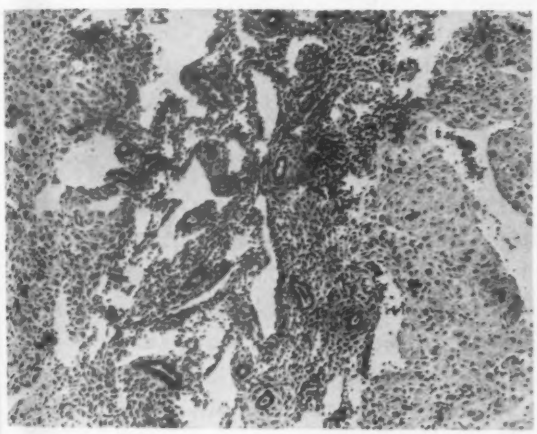

Fig. 3. Curettage specimen showing deciduoid endometrium bordering upon a zone of dilated tortuous endometrial glands. The epithelium has undergone degeneration in several of these glands. (×75; reduced ⅓.)

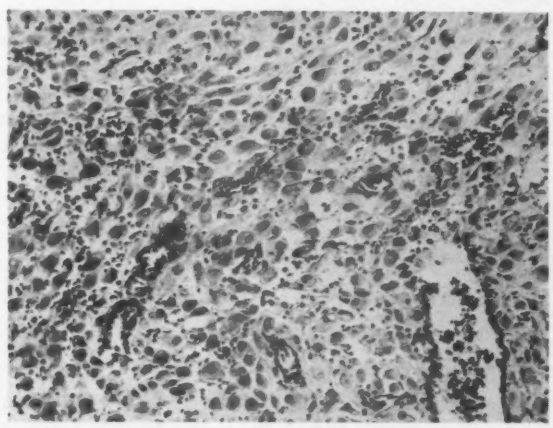

Fig. 4. Scraping from the endometrium showing edematous decidual stroma containing several tortuous endometrial glands with alteration of the lining mucosa and pyknosis of the nuclei. (×140; reduced ⅓.)

Fig. 5. Section from ovary of patient operated on after three months of therapy. Wall of follicle cyst showing areas of edematous ovarian stroma. The layer of granulosa cells adjacent to the follicle cyst show microcystic spaces filled with liquor folliculi. (×110; reduced ⅓.)

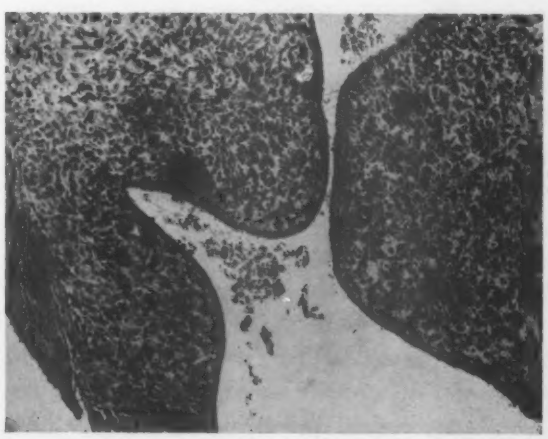

Fig. 6. Section from the surface of an ovary after three months of therapy showing decidual tissue with inflammatory cellular infiltrate replacing an area of endometriosis. Several degenerated endometrial glands with pyknotic nuclei are noted. (×140; reduced ⅓.)

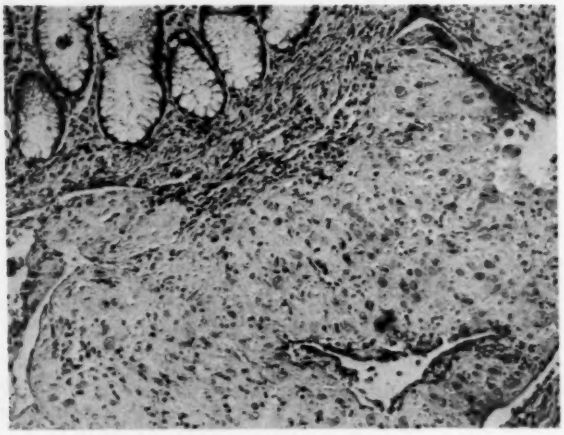

Fig. 7. Effect of norethynodrel on ectopic endometrium. Section shows colonic mucosa beneath which the submucosa as well as the muscular wall is replaced by sheets of decidual stromal cells. Bottom portion of the section contains an endometrial gland with degeneration of the lining epithelium. The latter is low cuboidal and shows no secretory activity. (×120; reduced ⅓.)

Follow-up

Recurrences. Six of the 123 patients treated with norethynodrel were lost to follow-up during the projected course of therapy. Of the 83 patients re-evaluated, the average length of follow-up has been 5.4 months. It is doubtful whether any valid conclusions regarding recurrences can be drawn from those cases with a follow-up of less than six months. If we eliminate all patients followed to date for less than this time (55 patients), there remain 28 patients. Average length of follow-up for this group is 10.9 months. In 5 patients in this group (17.8 per cent) recurrences developed 4 to 11 months following an original 6 months of therapy. The average length of remission was 7.2 months. The average age of this recurrence group was 34 years. Two patients had minimal, 2 moderate, and one severe involvement at the time of the original diagnosis. All but one patient showed endometriosis of different organ structures from the original involvement. One of these patients was re-treated for an additional 6 months with norethynodrel and at culdoscopy again showed no evidence of disease. One is receiving a second course of norethynodrel at the present time. One required laparotomy and conservative operation. The 2 remaining patients are receiving courses of another of the newer progestational agents.

Menses following norethynodrel therapy. Following completion of the full course of therapy, all patients were requested to record their daily temperatures on basal body temperature charts with careful attention being placed on return of normal ovulatory patterns. After culdoscopy and curettage, light bleeding continued up to 10 days and was generally associated with minimal cramping. The first menstrual period was usually delayed, appearing 4 to 8 weeks after withdrawal of the medication. This was characterized as being heavy and often lasting 6 to 10 days. Subsequently, normal ovulatory cycles returned.

Pregnancy following norethynodrel therapy. Four patients became pregnant after norethynodrel therapy. The duration of therapy in each instance was 6 months. Thirty-eight, or 46 per cent, of the 83 patients re-evaluated gave a history of infertility (2 to 16 years). All of the patients who have become pregnant were in this infertile group, with periods of infertility of 3, 4, 8, and 9 years.

Comment

This preliminary report of our experience with norethynodrel over a 2 year span has aroused a new interest in our diagnosis and management of endometriosis. We have undertaken this study to determine the effect of the drug on the disease process and to evaluate its concomitant side effects. We are not proposing that all patients with endometriosis be treated in the manner which has been outlined. Certainly, in the younger age groups, pregnancy, when possible, is preferable. In 77.7 per cent of all patients after 6 months of therapy there has been a complete regression of disease. Only 12.4 per cent have shown no improvement. Visible results were approximately the same regardless of the severity of the disease or the age of the patient.

The unpleasant side effects were those

often seen in pregnancy, although frequently they were more pronounced. Abdominal cramping, breakthrough bleeding, and especially nervousness and irritability made this method of therapy disagreeable to the majority of patients. Tranquilizers were frequently necessary for the latter complaint. Leg cramps, vaginal discharge, and abdominal fullness were other distressing aspects. Considerable encouragement had to be given in order to persuade many patients to remain on the therapy for 6 months. In a few patients, swings in libido developed, although most were not affected in this manner. Many patients did admit to being more relaxed with coitus due to improvement of previous dyspareunia and, in some cases, to the loss of fear of becoming pregnant.

We were impressed with the number of patients who were emotionally disturbed during treatment. In each instance this probably represented an accentuation of a basic emotional instability. We have frequently wondered if there is not a neurotic personality-type in which endometriosis is more prone to develop. Five of our patients became so severely disturbed that psychiatric treatment was necessary during the course of therapy.

Weight gain was a pronounced and constant feature in the group. Pelvic findings during therapy were strikingly similar to those in early pregnancy. The cervix became soft, cyanotic, and markedly decidual in appearance. The uterus softened and enlarged to at least the size of a 6 to 8 weeks' gestation. Some patients also exhibited rapid and marked enlargement of known myomas and, in some, myomas were first noted only after norethynodrel therapy. Similar observations have been noted by Andrews and associates.[2] Regression was uniformly noted after discontinuation of therapy, and no instances of degeneration of myomas were noted.

Initially, in the study, we were treating patients with the smallest dose necessary to prevent breakthrough bleeding. In these first few patients there was minimal uterine enlargement, and, after several instances of incomplete regression, we increased the minimal maintenance dosage to 30 mg. daily, and more recently to 40 mg. Patients showing minimal uterine enlargement on this dose were treated with gradually increasing amounts until the uterus was at least 8 weeks gestational size. Using this regimen, we have become impressed with the observation that a good norethynodrel response in ectopic endometrium is mirrored by significant uterine enlargement.

We have been able to corroborate the experience of others that pregnancy does not occur during norethynodrel therapy.[6] We have proved to our satisfaction that the drug is safe in high doses, even up to 100 mg. daily, and for periods up to 15 months of continuous therapy. There were no abnormal cytological findings in this group and no permanent sequelae have remained following discontinuation of the drug. We agree with other reports[7, 8] that, after withdrawal, normal ovulatory periods recur. Our pregnancy rate following therapy is small, but our average follow-up period has been too short for valid conclusions.

We are unable to confirm the belief[2] that adhesions due to endometriosis are softened during therapy, although we suspect this to be true. Only a few patients in our series have undergone major surgical procedures during treatment, and, so far, our observations have been inconclusive.

Our recurrence rate of 17.8 per cent in the 28 patients followed for more than 6 months after therapy is not discouragingly high. This is in a small group, however, and it is anticipated that in a future report a more meaningful recurrence rate will be available.

At present, the cost of prolonged norethynodrel therapy, such as that undertaken in this study, is considerable. Such a plan of medical management, however, warrants consideration in those patients in whom we can reasonably expect to avoid major operative procedures.

Summary

1. One hundred and twenty-three patients diagnosed by culdoscopy and/or lap-

arotomy as having endometriosis were given continuous norethynodrel therapy.

2. Eighty-one patients were re-evaluated surgically, primarily by culdoscopy, after one to 6 months of continuous norethynodrel therapy. In this group the initial regression rate was 77.7 per cent. Except in 4 instances, all patients were treated for at least 6 months. Treatment was continued in some patients who showed incomplete regression. After an additional 6 months, these were again evaluated surgically. Only one patient was treated longer than 12 months. Of 83 total patients so evaluated after up to 15 months of continuous norethynodrel therapy, complete regression was obtained in 66, or 79.5 per cent. The average duration of therapy was 6.3 months.

3. With this type of therapy, regression of disease does not seem to be dependent upon its severity or the age of the patient.

4. Average norethynodrel dosage was 49.2 mg. per day, with maximum dosage being limited to 100 mg. per day.

5. Norethynodrel produces effects similar to pregnancy, but with several disagreeable side effects, including irritability, nervousness, and abdominal cramping.

6. No definite evidence of androgenic effect has been demonstrated.

7. Twenty-eight patients have been followed for more than 6 months after completion of therapy, with recurrences developing in 17.8 per cent.

8. Menses resumed a normal ovulatory pattern after cessation of therapy.

9. Of the 83 patients in the re-evaluated group, the average follow-up has been 5.4 months. Pregnancy has since occurred in 4, all of whom were previously infertile for periods of 3 to 9 years.

10. Norethynodrel has been shown to be a valuable adjunct in the treatment of endometriosis, especially in patients in whom we wish to avoid major operative procedures.

We wish to thank Dr. J. William Crosson of G. D. Searle & Company for generously supplying us with the Enovid used in this study, and Dr. Robert Kistner for his help and encouragement in the preparation of this paper.

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Cholesteatomatous endometriosis

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CHOLESTEATOMATOUS change in normally situated endometrium is rare, and as far as we know only 2 authentic cases have been reported in the literature.[5, 8] Motyloff[8] prefers the term "cholesteometra" for these cases to "cholesteatoma of the uterus" as originally proposed by Kaufman.[5] We have failed, however, to find in the literature a case similar to the one reported here in which cholesteatomatous change occurred in ectopic endometrium. An endometrial carcinoma was also present and caused the patient's presenting symptoms.

Case report

The patient, a 61-year-old white widow, was admitted to the hospital because of "crampy" lower abdominal pain and vaginal bleeding of one day's duration. An uneventful menopause had occurred at the age of 51. Menses began at the age of 13 and changed from 3 days every 28 to 5, 6, or 7 days every 28 after the birth of the first child, and some pain occurred on the fourth day after the birth of the fourth child. When the patient was 26, dilatation and curettage was performed for an incomplete abortion. A goiter developed after she had the fourth child; it disappeared with iodine therapy. Mild diabetes had been present for the past 5 years. The patient weighed 120 pounds when she had her first child and 165 pounds when she had her last. With treatment for the diabetes she lost weight and at the time of admission she weighed 112 pounds. The patient was para v, gravida vi, and all of the children were alive and well. The past history and family history were not otherwise remarkable.

From the Pathology Department of the Pittsfield General Hospital.

Physical examination outside the pelvis was essentially negative. The abdomen was soft and there was no tenderness or palpable mass. There was bleeding from the external cervical os, and the uterus, on bimanual examination, appeared slightly enlarged, soft, and boggy. The adnexa were not felt.

Dilatation and curettage 48 hours after admission yielded about 30 c.c. of uterine curettings which, on section, showed adenocarcinoma of the endometrium. Six days after curettage a total hysterectomy with bilateral salpingo-oophorectomy was performed. At operation the entire pelvic peritoneum appeared black and nodular, suggesting very extensive endometriosis. The deposits involved the pelvic floor, the fundus of the uterus, both tubes and ovaries, and the omentum. The fundus was enlarged to the size of a 2 months' pregnancy and appeared succulent. In addition to total hysterectomy and bilateral salpingo-oophorectomy, several endometrial implants including one from the omentum were excised for histologic examination. The patient made a good recovery from the operation and, at the time of writing, 21 months after operation, she is alive and well.

Gross description. The specimen consisted of a totally extirpated uterus (13 by 7 by 5 cm.) with both tubes (each 5 by 0.5 cm.) and ovaries (each 3 by 2.5 by 2 cm.) attached. Over the serosa of the uterus, the proximal ends of the Fallopian tubes and one ovary were numerous irregular soft greenish brown, dark brown, or dark red masses ranging from 0.1 to 2 cm. in greatest dimension. On section the myometrium measured 2 cm. in thickness and the cavity appeared markedly dilated. Almost the entire endometrium had been converted into finely granular yellowish gray material that varied from 0.1 to 0.3 cm. in thickness but did not appear to involve the underlying muscle. The

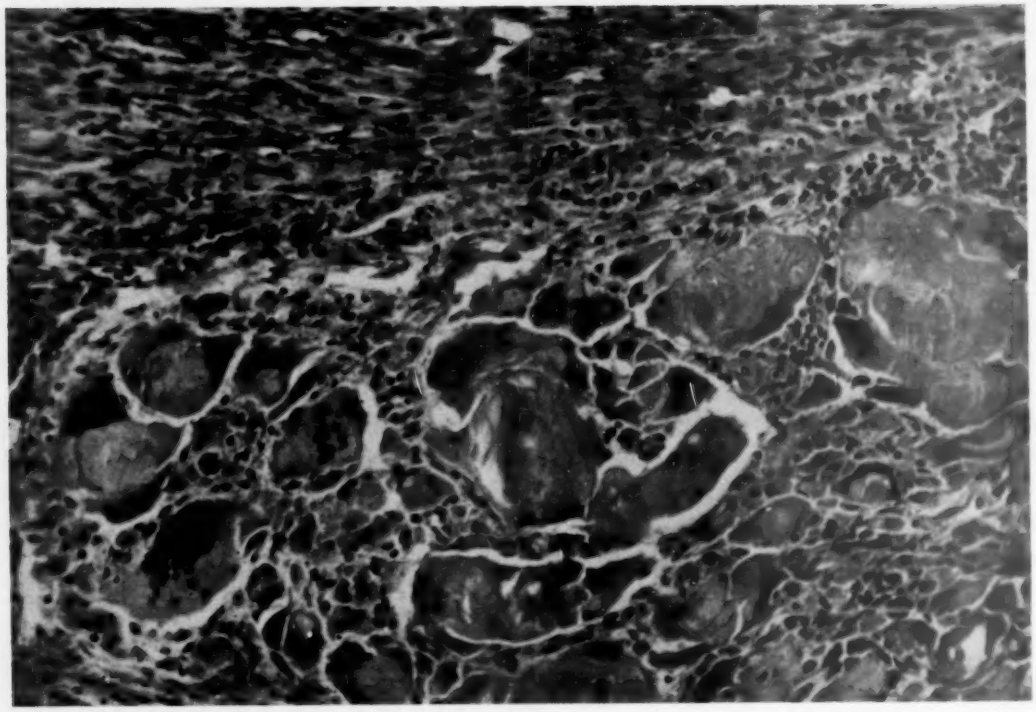

Fig. 1. Myometrial nodule showing pigment-laden macrophages and clumps of keratin. The latter contain faint outlines of squamous epithelial cells and are surrounded by multinucleated foreign body giant cells. (Hematoxylin and eosin. ×130; reduced ¼.)

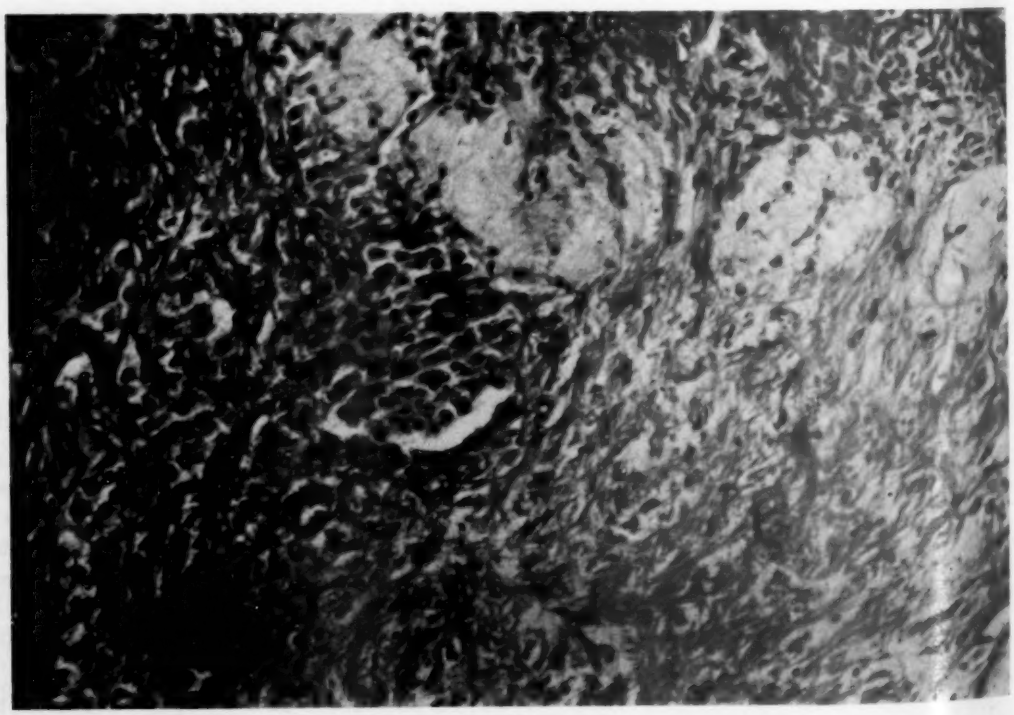

Fig. 2. Mass of epithelial cells arising just beyond fibrohyalinized part of a corpus albicans. (Hematoxylin and eosin. ×130; reduced ¼.)

myometrium contained numerous grayish green soft nodules ranging from 0.1 to 0.3 cm. in diameter forming in one area a confluent mass about 3 cm. in greatest dimension.

Histology. There was chronic cervicitis with epidermidization and atypia. The endometrium showed a well-differentiated adenocarcinoma with infiltration of the innermost muscle. There was squamous metaplasia of the endometrium with direct transition between the squamous cells and the carcinoma cells. The noncarcinomatous endometrium showed areas of postmenopausal hyperplasia, squamous metaplasia, and cholesteatomatous change similar to that described below in the myometrium and serosa. The myometrial pigmented nodules (Fig. 1) consisted of accumulations of macrophages, multinucleated foreign body giant cells, intra- and extracellular brownish pigment, and eosinophilic material shown to be keratin. This latter showed faint outlines of squamous epithelial cells without intercellular bridges and was surrounded by macrophages and giant cells. The macrophages had numerous intracytoplasmic brownish granules, and the giant cells had a brownish and/or eosinophilic cytoplasm due to the contained pigment and keratin. Endometrial stroma was seen in some of the lesions and in others there were typical endometrial glands. Direct change of the heterotopic endometrial glands or stroma into squamous epithelium was not observed. In places the carcinoma and pigmented nodules "collided." The subserosal pigmented nodules were similar but more vascular.

The mucosal folds of the tubes were distended with pigmented macrophages and giant cells, but cornified epithelial cells and keratin flakes were scarce. Similar accumulations were present in the muscle of the tubes. The tubal epithelium was of varying height, but the most common shape was cuboidal. Ciliated cells were few and peg cells scanty. Some nonciliated cells showed secretory activity and others showed nuclear overlapping and pseudostratification.

Sections of the ovaries stained with hematoxylin and eosin showed a whorled pattern of proliferating stromal cells with some partly fibrotic areas. Large polygonal epithelial cells with well-demarcated boundaries were scattered singly and in groups and masses throughout both cortex and medulla. Their plentiful deeply eosinophilic cytoplasm stained positively with oil red 0 and in most cases contained abundant finely granular brownish pigment. The nuclei were rounded, contained a slightly oxyphilic nucleolus, and the nuclear chromatin was evenly distributed. One such mass was seen arising from a corpus albicans in the region corresponding to the theca interna of the mature follicle (Fig. 2). There were transitions between the resting stromal cells and the epithelial cells via the actively proliferating stromal cells. A few cortical granulomas of Hertig were seen. Hilus cells were present in the hilus and mesovarium of both ovaries, and there were also some simple and germinal inclusion cysts.

Table I

Stain	*Pigment*	*Giant cells*	*Squamous epithelial cells and keratin*
Iron	+	–	–
PAS	++	++	–
Oil red 0	++	++	–
Sudan black	++	++	–
Schmorl's	+	+	–
PTAH	–	–	+
van Gieson's	–	–	+
Alcian blue	–	–	–
Thionin	–	–	–

Histochemistry. The histochemical findings are summarized in Table I. In the macrophages the pigment contained a little free iron but much less than is usually seen in endometriosis deposits before the menopause. The pigment was, however, strongly positive with periodic acid–Schiff, oil red 0, and sudan black stains, and moderately positive with the Schmorl's stain. The giant cells that showed brownish pigment with the hematoxylin and eosin stain were strongly positive with the PAS, oil red 0, and sudan black stains, and moderately positive with the Schmorl's stain. The extracellular pigment had the same staining properties as that in the macrophages and giant cells. The keratin and squamous epithelial cells were strongly stained by the phosphotungstic acid–hematoxylin and van Gieson's stains. The pigment was not stained with either the Alcian blue method or the thionin stain. These results indicate that the pigment is mainly lipofuscin. Plain birefringence is observed in areas corresponding to the cholesterol clefts and the keratin.

Comment

This case was one of cholesteatomatous change in endometriosis interna and externa associated with carcinoma of the endometrium and hyperthecosis of the ovary. Endometriosis and diabetes, both of which were present, were considered by Shippel[13] to be etiological factors in the development of hyperthecosis of the ovary. Hypothyroidism is also said to be a factor, and there was a history of a goiter in this case but no positive evidence of hypothyroidism. However, further questioning of the patient after operation did not disclose any other of the causes that Shippel lists. All of her children were breast fed until they were about 18 months old and menstruation did not recur during this time; there was no history of dyspareunia, loss of libido, or hirsutism.

Since 1941 several papers have appeared in the literature dealing with the possible correlation between ovarian hyperthecosis and endometrial carcinoma.[4, 10, 14, 15] The ovarian cells have been thought to produce estrogens which stimulate the endometrium and result in carcinoma. Roddick and Greene[11, 12] found no such correlation; McBride[7] denied, and Larson[6] found only meager evidence, that estrogens were implicated in the etiology of endometrial carcinoma.

Estrogens are known to be excreted long after the menopause and there is evidence of hyperestrinism in many patients with endometriosis.[3] However, although the epithelium in the Fallopian tube may respond to estrogens after the menopause as indicated by the occurrence of hyperplasia of the endosalpinx in patients with a feminizing tumor of the ovary,[7] the appearances of the Fallopian tube in carcinoma of the endometrium show no more evidence of estrogen stimulation than the tubes of healthy postmenopausal women.[1] The tubal epithelium, in our case, may well have been modified by the unusual changes in the mucosa, but the presence of some secretory cells suggests the influence of a hormone with some progesterone-like activity.[9]

Squamous metaplasia of the endometrium can be produced experimentally in animals by estrogens, androgens, or a mixture of estrogens and progesterone.[2] Hyperthecosis of the ovary and theca cell tumors may be associated with either masculinization or feminization, and the theca cell appears capable of producing estrogens, androgens, and progesterones. It is tempting to assume that such a theca cell hormone may have been responsible for the changes noted in this case.

It is our suggestion, therefore, that the ovarian hyperthecosis may have arisen in response to the presence of endometriosis and diabetes, and the hormone or hormones produced by the ovarian cells may have caused the squamous metaplasia and adenocarcinoma in the normally situated endometrium, and the squamous metaplasia and subsequent cholesteatomatous change in the endometriosis deposits.

Summary

A case of extensive pelvic endometriosis in a postmenopausal woman is described. Most of the endometrial deposits had become "cholesteatomas" as the result of squamous metaplasia and keratinization of the endometrial epithelium. This appears to be the first description of this phenomenon. An associated carcinoma of the endometrium caused the presenting symptom of vaginal bleeding. Possible explanations for these observations are discussed briefly.

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Injuries of the bladder

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THE injury I propose to discuss is the vesicovaginal fistula. The question at once arises, "How and why should this injury occur?" Putting aside rare causes, such as fractured pelvis or penetrating wounds, and excluding advanced malignant disease, there are three main types: those caused by obstetrical injury, those caused by gynecological operation, and those caused by overintensive radium treatment of cervical carcinoma.

Obstetrical injuries

As everyone knows, this was the usual reason for a fistula in days gone by, and it still is the major cause in those countries where obstetrical services are poorly developed, and cesarean section is beyond the reach of the average woman in labor. Those who have never worked in those distant lands, for example, the Sudan, Nigeria, and parts of India, can form no idea of the plight of the woman in obstructed labor—the calamity of the ruptured uterus, the gas-distended fetus, the bladder already torn or ready to slough should the patient survive delivery.

But here I must avoid self-righteousness. Obstetrical injuries of the bladder still sometimes happen in my country and have even happened in my own clinic. I have had it suggested to me that this must be because we in Britain still support midwives in our midst and because many of our deliveries take place without the presence of a physician. This, however, is a complete misjudgment of the situation. The midwife, as we use the term, is a highly trained nurse who has had extensive theoretical and practical training in obstetrics and has in fact had a much fuller experience of the work than has the young medical graduate who passes into general practice. No, the true answer is one which implicates all of us as teachers. Almost all the cases which have been referred to me have been caused by the failure of the attending doctor to detect disproportion—pelvic contraction, hydrocephalus, and the like—with the result that he attempts to deliver the baby with forceps when vaginal delivery is impossible. It is a deplorable fact that so many doctors, having applied the forceps blades, feel themselves irrevocably committed to deliver the baby, and will not give up the effort even when it becomes obvious that only by brute force can the baby be extracted (Table I, Figs. 1, 2, and 3).

Sometimes the nature of the damage is not at once obvious, and it is not until some days have elapsed that a portion of the bladder trigone sloughs and urine escapes. Those cases may be the result of prolonged compression of the bladder between the pubic symphysis and the fetal head, and they are therefore caused by delay in delivery rather than of brutal intervention —but too often these errors are combined.

This is an unhappy story; but I hasten to add that if the obstetrical utopia is still a long way off, it is much nearer than it was even 10 or 15 years ago; and the particular tragedies to which I have referred are becoming increasingly rare.

Presented at a meeting of the New York Obstetrical Society, Oct. 13, 1959.

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Operative injuries

This is by far the largest group (Table II). It would be presumptuous to attempt a complete analysis of the cause of injury; instead I shall put forward some ideas that I have formed after many years' work.

Total hysterectomy is the most common operation involved; and the usual cause of trouble is a tearing of the bladder during its dissection from the cervix and upper vagina. Please note the use of the word "dissection," for this exactly describes what should be done and implies the use of sharp instruments under careful inspection. The inexperienced surgeon is too often afraid to cut, however; instead he uses gauze pads or, worse still, wraps a gauze swab over his finger and blindly pushes the bladder down. The result is a tearing; and tearing means bleeding; and bleeding means failure to see; and failure to see means that the tear is not sutured there and then. I admit that the circumstances may be difficult. Endometriosis may be present; myomas may distort the uterus and cause the bladder to be unexpectedly elevated; or a previous operation may have played havoc with normal anatomy. Any or all of these complications may be present; but one thing is inexcusable and that is the failure to look for a possible bladder injury after a difficult hysterectomy. And here I would commend the simple procedure of injecting a methylene blue solution into the bladder and inspecting for possible leakage during the course of the operation (Fig. 4).

While a simple explanation can be found for most bladder injuries, cases undoubtedly occur in which a fistula appears when least expected. I believe that the explanation is a persistent oozing of blood between the bladder and the sutured vaginal wall. A hematoma forms, infection follows, and the resulting abscess erodes into the bladder on the one side and into the vagina on the other. With this danger in mind, it is my practice to leave a small portion of vaginal wall deliberately unsutured, to act as a safety-valve for any accumulation of blood; this

Table I. Obstetrical causes of 62 fistulas

Prolonged labor or forceps delivery	56
Cesarean section	3
Rupture of uterus	2
Symphysiotomy	1

Table II. Gynecological causes in 163 cases

Hysterectomy, abdominal or vaginal	69
Wertheim operation with or without radium	11
Radium alone	12
Colporrhaphy, including Manchester operation	33
Millin or Aldridge sling, vesicolysis	8
Congenital abnormality	5
Abdominoperineal resection of rectum	4
Bladder neck resection in infants	3
Neglected cup and stem pessary*	3
Ulceration of obscure origin	2
Removal of cervical stump	2
Miscellaneous	11
Neglected contraceptive appliance†	
Amputation of cervix uteri	
Fractured pelvis	
Urethral diverticulum	
Vaginal cyst	
Diathermy of bladder papilloma	
Myomectomy	
Vaginal fixation	
Cystectomy after radium	
Cotton reel in vagina	
Self-inflicted wound	

*In one case this had been left in position for 39 years.
†Intrauterine "wishbone" left in position for 32 years.

Table III. Duration of fistula

Up to 7	188
8-10	10
11-20	8
21-24	12
25	2
27	1
28	1
32	1
38	1
44	1

Table IV. Number of previous operations*

0	74
1	57
2	27
3-5	39
6-8	7
9-11	3
12-13	3
17	1
18	2
19	1
Not stated, or "many"	11

*Over one third were transvesical or transabdominal.

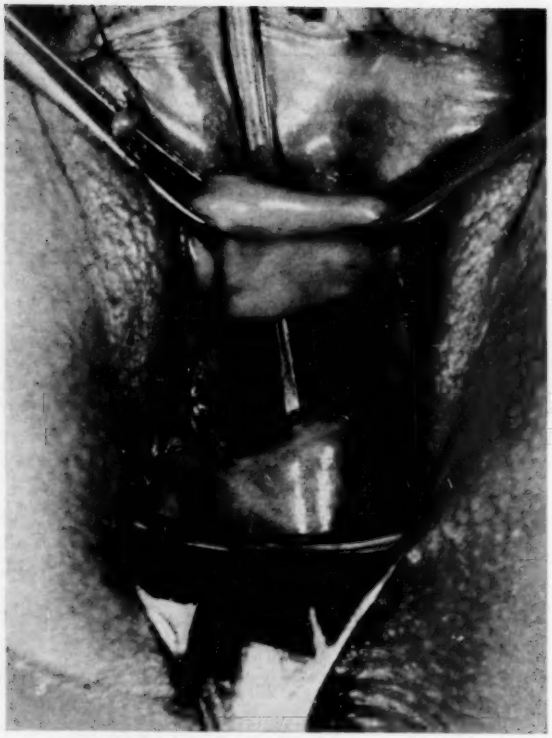

Fig. 1. A large vesicovaginal fistula of obstetrical origin. There had been a prolonged labor followed by a forceps delivery of a very large fetus.

Fig. 2. The same case as that shown in Fig. 1; the ureter is indicated by a probe.

applies equally to abdominal and to vaginal hysterectomy.

A word on ureteric fistulas seems appropriate at this point. Injury to the ureter is usually supposed to be caused by a carelessly placed clamp at the side of the cervix. This may of course be an explanation, but I incline to the view that a more common cause is an insufficient clearance of the bladder from the sides of the cervix and vagina. When, subsequently, the surgeon severs the uterus from the vagina, he unwittingly snips or cuts into the ureter where it lies at the lateral angle. Another cause, insufficiently appreciated, is that one woman in 20 has a double ureter; the surgeon may then carefully preserve one organ but unknowingly injure the other.

Dislocation of the ureter from its normal position in the broad ligament by fibroid tumor or cyst is another well-known cause of accident.

Colporrhaphy, as will be seen from Table II, is another important and perhaps unexpected cause of vesicovaginal fistula. There is no doubt that most cases occur in the hands of inexperienced surgeons—but not always. As in the case of hysterectomy, there is inherent in colporrhaphy the danger of hematoma formation with subsequent infection and necrosis (Fig. 5).

Another cause is a rough, deep dissection which leaves the urethra almost denuded. In such cases the slightest roughness in subsequent catheterization may cause the instrument to burst through the urethra into the vagina, usually at a point just short of the vesicourethral junction.

Radium injury

This is without question the most difficult form of vesicovaginal fistula to treat, and some cases, it must be conceded, are untreatable by any direct method. In all radium injuries to the bladder there are uncertainties to which an answer must be attempted. Is the original disease still active? Has the radium necrosis run its course or is it still extending? How "clean" or otherwise are the fistula margins? Is the vagina

stenosed, or are the affected structures uncompromisingly fixed at a high level? Finally, are both kidneys active and are both the ureters normal in size?

It would take me too far from the main topic to discuss these cases further. Suffice it to say that if direct repair is out of the question a high colpocleisis, in which the anterior and posterior vaginal walls are united just below the level of radium fibrosis, may be effective. If, as is sometimes the case, there is also a high rectovaginal fistula, an inguinal colostomy with closure of the lower loop may be performed. The colpocleisis then serves to direct the urine into the empty rectum, where it is controlled by the anal sphincter.

Identification of the fistula

To discuss the ways and means of identifying a fistula may seem an elaboration of the obvious. So it is when the fistula is large and permits the passage of one or even two fingers into the bladder. But, at the other extreme, the fistula may be so small or its track so tortuous that detection is far from easy. It is then necessary to inject a strong methylene blue solution into the bladder and to inspect with great care, using retractors to stretch and to display to the fullest extent every part of the anterior vaginal wall.

The three-swab test is sometimes helpful. After a colored solution is injected into the bladder, 3 plugs of cotton wool are inserted tandem fashion into the vagina. The patient then walks about for 10 or 15 minutes. If after that time the lowest swab is found to be colored, the leakage is from the urethra, and the patient presumably has stress incontinence of urine; if the middle or upper swab is colored the patient has a vesicovaginal fistula; if the upper swab is wet but not colored the leakage is from a damaged ureter.

When a patient with a fistula is being examined there are two important things to keep in mind:

1. Not infrequently more than one fistula is present. This should be looked for when

Fig. 3. A vesicocervical fistula. A deeply split anterior lip of the cervix is held upward by a vulcella. The upper sound is inserted into the fistula; the lower sound indicates the uterine cavity.

Fig. 4. A typical posthysterectomy fistula. The opening in these cases is usually far above the bladder trigone.

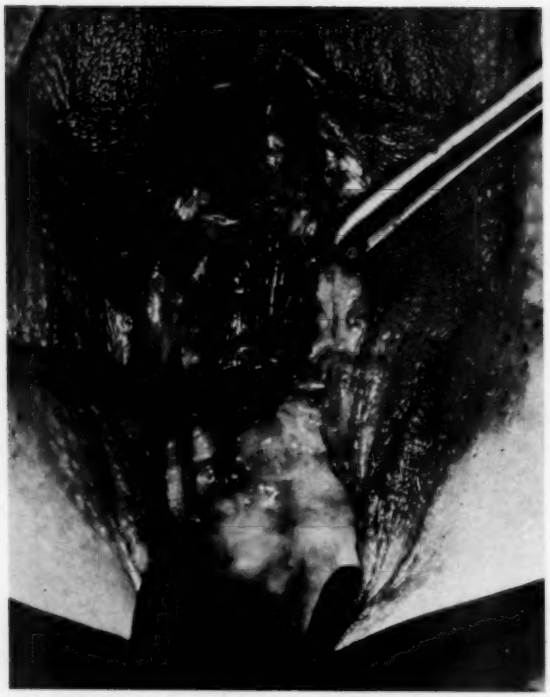

Fig. 5. Complete destruction of the urethra with a "gutter" of mucosa exposed. A sound indicates the opening of the bladder.

there has been a previous attempt at closing a large fistula. A residual leakage is then perhaps seen, and the small opening is in due course repaired. But the patient is no better, and she believes that the surgeon has again failed to effect a cure. In fact, one hole has been well and truly repaired, but another opening, some distance from the first, has been overlooked; and it is from this second opening that the leakage is occurring. I have seen several such cases.

2. The other elusive feature is a ureter which opens at the margin of a large fistula. The surgeon successfully closes the bladder, but the patient continues to be "wet." He has failed to notice the ureter which as the result of his operation now drains directly into the vagina. Parenthetically, I may mention that such conditions can often be alleviated by a vaginal plastic operation, the ureter being turned inward toward the bladder and kept temporarily in that position by a ureteral catheter while the vaginal wall is firmly united over the partly repaired bladder. In this connection I need scarcely mention that a full investigation of the function of both kidneys should be made before reparative work of this nature is undertaken.

Operative technique

I have elsewhere[1, 2] described my technique and need not repeat the details now. In all but one case the vaginal approach has been used, although in odd cases of vesicocolic or vesicorectal fistulas (following hysterectomy) an abdominal operation was, of course, necessary.

The repair is usually made from side to side, but in exceptional cases a direction transverse to the vaginal axis is preferable if the resulting tension is thereby lessened. As explained elsewhere, the vaginal walls are undercut only so far as to allow satisfactory suturing. Any tension caused by the repair is later corrected by relaxation incisions made well to the side of the repair.

On three or four occasions I have found the Martius procedure useful in providing an extra covering for a repaired urethra when the vaginal wall has been insufficient. A pedicle of vascular fatty tissue is mobilized from the fold of the labium majus,* is passed through a tunnel below the vaginal wall and stitched into position over the repaired urethra.

When the fistula involves the vesicourethral junction, or when the whole urethra has to be reconstructed, it is important to use 2, or possibly 3, separate catgut sutures to build up the muscle of the sphincteric area of the bladder.

Drainage is maintained for 14 days, usually by means of a polyvinyl tube with extra "eyes" cut in the side, which is anchored to the external urinary meatus. If, however, this tube (or any other type of catheter) begins to cause pain after 6 or 7 days it must at once be removed and another type (e.g., a Foley catheter) substituted. This symptom, with or without accompanying hematuria, may be caused by a pressure-

*_Not_ the labium minus, as erroneously stated in the first reference given.

ulcer forming where the tip of the catheter impinges on the bladder trigone.

The unabsorbable nylon sutures are removed after the twenty-first day.

Results of treatment

Over a period of 25 years I have dealt with some 250 cases of vesicovaginal fistula, rectovaginal fistula, or allied injury. Many of these were of long duration (Table III) and numerous attempts at repair had been made previously (Table IV). I have perhaps become dogmatic on some points, but I am certainly open-minded on others. I would say, and say deliberately, that the traumatic vesicovaginal fistula is an eminently curable lesion. In more than 190 cases of true vesicovaginal or urethrovaginal fistula a successful closure has been effected in each case and usually with complete restoration of normal function. In a small minority—well under 10 per cent—there has been some residual stress incontinence of urine; a disability which is, however, trivial compared with the previous constant wetness.

In a further 20 or 30 cases of complete urethral destruction, radium damage, or other extensive or complicated injury, the functional results have of course been less consistently good; but even in these unpromising cases much improvement has usually been effected and in some a complete cure. In 4 patients (2 of them with congenital abnormalities of the bladder and urethra) a ureteric transplantation was advised, and it was performed in 3. These were the only cases in a series of 225 cases of urinary fistula in which this drastic procedure was required, although many patients had previously been told that only by ureteric transplantation could there be any hope of relief.

When the fistula is surrounded by pliable vascular tissue, its repair is usually easy and can be confidently undertaken by any experienced gynecologist. But when there is extensive scarring or high fixation, or if radium has been used, or previous attempts at repair have failed, the operative closure may be very difficult and should not be attempted unless the operator has had previous good experience.

Regarding technique, each worker must develop his own methods and learn the pitfalls and the tricks by which they may be avoided. He must be prepared to exercise infinite patience in technique. Equally important, he must keep the needs of each patient clearly in mind and be sufficiently pliable to adapt his technique to those particular needs. The work is exacting, but there is no greater satisfaction than to free the woman from her shame of urinary incontinence and to restore her to a full life in her family and social circles.

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Discussion

Dr. Henry Falk, New York, New York. There are two types of fistulas at the urethrovesical junction that we see. One, of which Professor Moir spoke, is the fistula resulting from the transvesical cutting through of "the bar" in the bladder. Last year in Chattanooga I saw 4 children, all under the age of 10, who had had bars cut transvesically which were followed by a fistula at the urethral vesical junction. I know of no more difficult place in which to repair a fistula, particularly in young children where there is so little tissue to work with. I am glad to hear that Professor Moir repaired 2 of these in children of 10 to 12 years of age, and I believe that it is indeed best to wait until the patients are this age.

The other fistula in this area is that following anterior vaginal repair. Here again we may not have sufficient tissue, and after the actual fistula

is cured the patient may require further surgical procedures for incontinence.

Still another type of fistula follows cesarean section. We have had 4 such fistulas, one in which the woman menstruated through the bladder for 25 years without any leakage of urine from the vagina. She came to us because she had developed fibroids and she could not pass the clots of blood coming from the uterus. In her case we did a total abdominal hysterectomy and after the uterus was removed the fistula was closed transabdominally in 3 layers and healed without any difficulty.

We have discarded the use of a dye to discover small fistulas. Methylene blue, when it comes into the operative field, colors it and may obscure the fistula. Consequently, we began to use milk—specifically boiled powdered milk. We believed we had a marvelous new idea until we read a paper by Professor Rose, written in 1890, in which he said he demonstrated 3 fistulas by the use of milk in the bladder.

There is one type of small vesicovaginal fistula that occurs after total abdominal hysterectomy about 14 to 20 days after the patient has gone home and is apparently well. I believe that these are probably due to a ligature which has required many days to slough through. We have cured 15 of these small fistulas, under 4 mm. in size by introducing an electrode through the bladder or through the vagina and coagulating the fistulous tract.

With regard to fistulas following total abdominal hysterectomy, these are always at the vault of the vagina and are always in front of the scar. When these patients are examined with the cystoscope, it is seen that these fistulas are about one half to three fourths of an inch above the trigone. It is very rare in the total abdominal hysterectomy to have it much lower than that.

When there is a question as to whether the fistula is vesical or ureteral, if the specific gravity of the urine appearing in the vagina is 1004, it is probably a ureteral fistula. The kidney with a ureteral injury is damaged, therefore causing the low specific gravity, whereas the specific gravity of the urine in the bladder which is coming from a fairly normal kidney will probably be 1014. We were able to make that differential diagnosis in this way in one of our cases.

When the loss of urethra is due to a surgical procedure, the operation may not be too difficult. Harris of Australia described an excellent procedure to be applied when the roof of the urethra is still present. However, when the loss of the urethra is the result of an obstetrical injury, where both the floor and the roof of the urethra are gone, and all that is left is scar tissue, you are called on to use all your ingenuity. The important objective is to give the patient a sphincter.

In all of our cases where we reconstructed a urethra, we have used a vaginal cystotomy to introduce a catheter into the bladder and to allow drainage for about 10 days. In only one instance have we had a fistula result after the removal of this catheter and that was because the patient developed thrombophlebitis and the catheter was allowed to remain in for 3 weeks.

It is absolutely essential for one to know every possible way of attack when a vesicovaginal fistula is present. After you have figured out exactly what type of repair you are going to use in a particular case, you may still find in the middle of the procedure that you have to completely reverse yourself and use an entirely different technique. Each case has its own peculiarities and must be studied for a long time.

Rarely you will find a patient who has a fistula that cannot be repaired, except, as Professor Moir said by closing the vault of the vagina and opening a passage into the rectum. We recently had such a case. The patient had had 4 operations and the bladder would now hold only 25 c.c. of urine. She also had a rectovaginal fistula at the vault of the vagina. A transverse colostomy was performed. After the colostomy the vesical symptoms cleared up and we were able to study the fistula. Knowing that we could not enlarge the bladder, we closed the vault of the vagina by means of a partial colpocleisis (Latzko technique). The patient now urinates from the rectum every 3 or 4 hours, and usually goes all night without any difficulty.

Dr. Albert H. Aldridge, New York, New York. In Professor Moir's experience, 70 per cent of the injuries which he treated were gynecological in origin and the majority were due to accidents and complications resulting from abdominal hysterectomy. In 1955 Everett reported on 173 urinary tract injuries which had been treated during a 20 year period at Johns Hopkins. In his series, two thirds of the ureteral injuries, two thirds of the bladder injuries, and three fourths of the vesicovaginal fistulas had occurred following hysterectomies for benign

uterine conditions. He emphasized the risk of such injuries in women who had intraligamentous tumors or cysts and in those who had adhesion-producing conditions such as pelvic inflammatory disease or endometriosis.

From our experience at the Woman's Hospital we are convinced that most of the injuries to the urinary tract resulting from hysterectomy can be prevented. We believe it is important to maintain upward traction on the uterus while dissections are being carried out in natural planes of cleavage. All pedicles should be tied securely. Some ureteral injuries and ligations occur as a result of efforts to control bleeding in the broad ligaments which develops as a result of misplaced ligatures. Late injuries may be due to infected hematomas in and about the vaginal vault which have resulted from inadequate hemostasis at time of operation. We believe the incidence of postoperative tissue sloughs in the vaginal vault can be reduced by adoption of surgical techniques which involve as little damage as possible to the blood supply to structures in and about the vault.

Following tradition at the Woman's Hospital, I learned first to close fistulas by the classical Sims technique, using silver wire sutures. Subsequently, I came to prefer separation of the bladder wall and its fistulous opening from the wall of the vagina and to close a fistula by 2 or more layers of tissue using chromic catgut sutures. By this routine, tension on the margins of a wound can be reduced and superimposition of lines of sutures can be avoided. Solid closures produced by such techniques seem to promote prompt and more certain healing.

Collins at Tulane has recommended the use of cortisone and antibiotics to eliminate infection and induration about the margins of a fistula. By this routine he has found that fistulas can be successfully closed at about 10 to 14 days after they occur. This offers a possible means by which prolonged periods of discomfort for patients can be eliminated. It may also reduce the incidence of medicolegal complications resulting from such problems. I have had one satisfactory result following the preoperative treatment recommended by Collins.

The surgical techniques and principles adopted by Professor Moir for closure of fistulas are similar to those developed by the pioneer surgeons who first proved that vesicovaginal fistulas could be closed. He has emphasized the importance of excision of all scar tissue and a wide area of denudation about the margins of a fistula, placement of sutures down to, but not through the mucosa of the bladder, and steps to prevent tension on the lines of sutures. Refinements in technique which he has developed include the use of nylon sutures to close fistulas and polyethylene tubes and suction for postoperative drainage of the bladder.

Dr. Louis M. Hellman, New York, New York. The operation which has most distinguished our specialty is not perhaps hysterectomy or repair of vaginal relaxation but actually the operations on the lower urinary tract. These of course stemmed from Sims and were taken up by Kelly in Baltimore and further developed by Norman Miller, Albert Aldridge, and Henry Falk in this country, but above all by Dr. Moir in England, who has operated on 250-odd cases. Perhaps it might be safe to suggest that there is nobody in America who has had such a vast experience.

OBSTETRICS

Variations of enzyme activities during normal pregnancy

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SOME attempts have been made in the past to study enzyme changes during gestation. Page[1] showed that plasma pitocinase increased one thousand fold from the fourth to the thirty-eighth week of pregnancy and that this high level was maintained during labor. Ahlmark[2] found a considerable increase in blood histaminase after the fifth week of gestation, which reached 500 to 1,000 times the normal in the later stages of pregnancy. Luschinsky[3] found that placental glutaminase activity decreased as pregnancy progressed. There have been many extensive studies of enzyme activity in the placenta, and this subject has been comprehensively documented.[4]

In a previous publication we presented studies of serum enzymes of mothers at term and in their newborn infants.[5] Esterases (cholinesterase, tributyrinase, and alkaline phosphatase) were found to be at higher levels of activity in the maternal serum at delivery when compared with that of their newborn infants. On the other hand, those enzymes which are known to be elevated in necrotic processes (aldolase, glutamic oxalacetic transaminase, and lactic dehydrogenase) were found to be present in higher amounts in the cord serum, the reverse of the situation with the esterases.

Because these previous findings are related to pregnancy at term and to the newborn infant, the question arises as to the changes in enzyme levels that may be seen starting in the early phases of pregnancy. The present study is concerned with an evaluation of the degree of activity of serum enzymes from the beginning of gestation to the time of delivery. The enzymes which are evaluated include the three esterases previously mentioned, as well as glutamic oxalacetic transaminase and lactic dehydrogenase. Here, again, the results show a pattern in which the esterases differ from the other enzymes

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in their activities during different stages of pregnancy. Cholinesterase and tributyrinase levels decrease during pregnancy, while transaminase and lactic dehydrogenase increase. Alkaline phosphatase shows the most change with a marked increase starting in the second trimester and continuing to very high levels at the time of delivery.

Materials and methods

Venous blood specimens were collected from women during various stages of their prenatal course, and within several minutes after delivery. All specimens were refrigerated immediately and determinations on the serum were carried out promptly, usually within 48 hours.

Cholinesterase was determined by the colorimetric procedure of Molander and colleagues[6] and the results were reported as ΔpH units. Tributyrinase was determined electrometrically by the method of Friedman and Shriro[7] and the results were reported as ΔpH units. Glutamic oxalacetic transaminase was determined spectrophotometrically by the method of Karmen and co-workers.[8] Lactic dehydrogenase was determined spectrophotometrically by the method of Wroblewski and LaDue.[9] Alkaline phosphatase was determined by the method of Shinowara and others[10] using glycerophosphate substrate buffered with barbiturate to a pH of 10.8. The results for alkaline phosphatase are reported in Shinowara-Jones-Reinhart (S.J.R.) units.

Results

Except for the alkaline phosphatase, which showed a marked increase in activity during pregnancy, the changes in the enzyme levels varied within a narrow range. Statistical variations, however, were evident when the gestation period was divided into the following stages: 4 to 15 weeks, 16 to 35 weeks, and 36 weeks to delivery. In the case of alkaline phosphatase, where the changes were more significant, the gestation period was divided into 5 stages.

Table I gives a summary of serum cholinesterase values during the three periods of

Table I. Cholinesterase in maternal serum at different stages of pregnancy (recorded in colorimetric ΔpH units)

	Gestation (weeks)		
	4 to 15	*16 to 35*	*>36*
Subjects	156	74	46
Total range	0.37-0.88	0.35-0.86	0.36-0.82
Average	0.661	0.612	0.618
S.D.*	±0.105	±0.095	±0.108
t	2.40		

*S.D. $\sqrt{\sum \frac{d^2}{n-1}}$

Table II. Tributyrinase in maternal serum at different stages of pregnancy (recorded in ΔpH units)

	Gestation (weeks)		
	4 to 15	*16 to 35*	*>36*
Subjects	156	71	45
Total range	0.41-0.90	0.35-0.90	0.42-0.84
Average	0.639	0.591	0.591
S.D.	±0.121	±0.132	±0.114
t	2.41		

Table III. Glutamic oxalacetic transaminase in maternal serum at different stages of pregnancy (recorded in spectrophotometric units)

	Gestation (weeks)		
	4 to 15	*16 to 35*	*>36*
Subjects	157	72	46
Total range	11-34	13-33	13-34
Average	20.8	21.8	23.8
S.D.	±5.7	±4.8	±5.4
t	3.20		

Table IV. Lactic dehydrogenase in maternal serum at different stages of pregnancy (recorded in spectrophotometric units)

	Gestation (weeks)		
	4 to 15	*16 to 35*	*36 to delivery*
Subjects	105	73	39
Total range	60-230	60-235	110-275
Average	151	145	192
S.D.	±42	±38	±43
t	5.15		

pregnancy. There was a significant lowering of activity from the sixteenth to the thirty-fifth week when compared with the values at the beginning of pregnancy. A calculated t of 2.40 and $P < 0.05$[11] indicates a significant decrease in cholinesterase activity as pregnancy progressed and reached its minimum before term since the level after 36 weeks' gestation showed no further decrease. It should be noted that these results are recorded in pH changes which are within a narrower range than direct alkali titration. The relation of pH change and titration of liberated acid gives the usual sigmoid curve[7] of a buffer titration; therefore, statistical changes based on titration would be even more marked than the pH changes recorded here. This consideration also holds for tributyrinase.

Table II for tributyrinase shows results similar to those for cholinesterase. The t of 2.41 between the early and middle period also gives a $P < 0.05$ and here, also, the minimum activity was reached before term as the levels after 36 weeks' gestation showed no further decrease. It is worthy of note that both cholinesterase and tributyrinase showed a further decrease in the cord serum.[5] There is some question as to whether one is measuring the same enzyme[12] with two different substrates, acetylcholine for cholinesterase and tributyrin for tributyrinase. Although the activity of these enzymes appeared to be identical in the serum it did differ in amniotic fluids[13] where tributyrinase was absent while significant amounts of acetylcholinesterase were found.

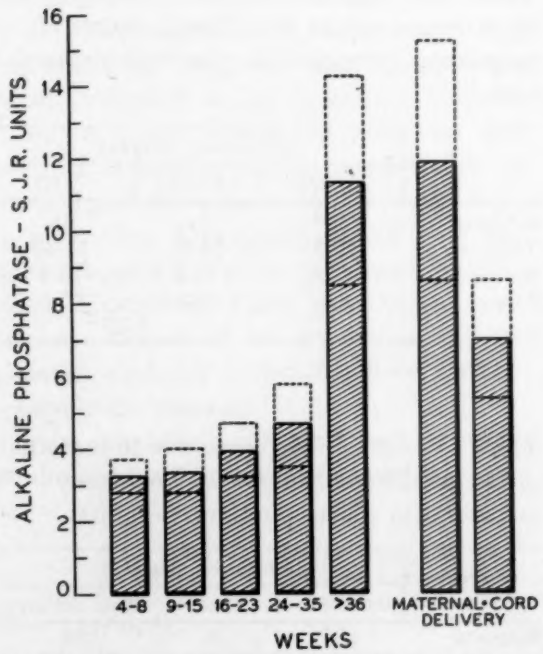

Fig. 1. Alkaline phosphatase at various stages of pregnancy and in the maternal and cord serum at delivery. Solid lines are average values; dashed lines include one standard deviation.

Glutamic oxalacetic transaminase (Table III) and lactic dehydrogenase (Table IV) showed a pattern different from the esterases during the course of pregnancy. The activity of these enzymes remained unchanged during the first 36 weeks of gestation and then rose significantly near term with a t of 3.20 for transaminase and 5.14 for lactic dehydrogenase, and $P < 0.01$ in both instances. In a previous study,[5] these enzymes were found to be further increased in the cord serum. The contrast with the esterases was striking.

Alkaline phosphatase (Table V) did not follow the pattern of the other esterases. A significant increase in activity was observed as early as 16 to 23 weeks' gestation, and there was a continuous increase until rather high levels were reached near term. The highest maternal activities were found at the time of delivery (Fig. 1), but the simultaneous cord levels were significantly lower than those of the mother. Apparently alkaline phosphatase has its own characteristic functions during the gestation period and differs from the other esterases studied.

The observation of unusually high levels of alkaline phosphatase at term in each of 3 successive pregnancies in the same patient is outlined here.

Patient B. L. was first seen at age 22 in November, 1956, as a nullipara; the expected date of delivery was June 19, 1957. She was a normal adult woman weighing 132 pounds. The prenatal course was uneventful. A living male infant weighing 6 pounds, 8 ounces, was delivered by low forceps on July 14, 1957. The maternal alkaline phosphatase serum level at delivery was 54.9 units, while the infant's cord blood serum

Table V. Alkaline phosphatase in maternal serum at different stages of pregnancy (recorded in S.J.R. units)

	Gestation (weeks)				
	4-8	*9-15*	*16-23*	*24-35*	*>36*
Subjects	76	40	53	22	48
Total range	2.2-4.9	2.3-5.0	2.2-5.8	2.7-6.5	6.8-17.4
Average	3.28	3.42	3.91	4.66	11.44
S.D.	0.58	0.66	0.87	1.17	2.88
t*	0.91	5.60	8.03	29.7	

*t compared with 4 to 8 weeks' gestation.

showed a level of 9.8 units. A determination of the mother's serum was made 3 days post partum and gave a level of 32.4 units.

The same patient's second pregnancy terminated in a normal spontaneous delivery at 40 weeks' gestation on July 25, 1958. At the twelfth week of this gestation the serum alkaline phosphatase level was 4.4 units, and at 38 weeks it had risen to 36.6 units. Specimens were not obtained at delivery. However, 5 days post partum the level was 18.7 units. X-ray films taken at this time were reported to Dr. Richard Friedenberg as, "Bone survey includes anteroposterior and lateral skull, left and right humerus, lumbar spine, pelvis, both hips and femora. All the bones show normal density and architecture. No evidence of osteoporosis."

The third pregnancy proceeded normally and the patient was delivered uneventfully at 40 weeks' gestation on Sept. 20, 1959. The maternal alkaline phosphatase level then was 36.7 units and the cord serum level 11.8 units. On Feb. 8, 1960, the patient's level was 5.2 units. Table VI contains a summary of the findings on this patient. The significance of these results will be discussed further in the next section.

Comment

Serum enzymes that are lower in the cord blood compared with the mother's at delivery, such as cholinesterase and tributyrinase, are likewise decreased in the mother during the course of pregnancy. Other enzymes, such as glutamic oxalacetic transaminase and lactic dehydrogenase, are increased in the maternal serum during pregnancy and reach the highest levels in the cord serum.[5, 14] Alkaline phosphatase has its own characteristic pattern, for it increases in the mother during pregnancy, but is lower in the infant's cord blood when compared with the mother's at delivery.

Pritchard[15] also found a decrease in cholinesterase during pregnancy and concluded that this reduction in activity was the result of the hemodilution of pregnancy. That this seems an oversimplification was apparent from the observation that transaminase and lactic dehydrogenase increased in the same individual despite hemodilution. Furthermore, at term when the hemodilution was greatest, the esterase activities did not decrease when compared with those of the middle period of gestation. Other factors such as activators and inhibitors, part of the enzyme systems, are more likely to influence enzyme levels. Tourtellotte and Odell[16] could not detect any acetylcholine inhibitors in maternal plasma and suggested that the decreased levels of cholinesterase during pregnancy were related to hemodilution or altered hepatic function.

It is of further interest that the two enzymes which have a comparatively higher activity in the newborn infants are the ones that are increased in the mother during preg-

Table VI. Alkaline phosphatase levels of Patient B. L. through three successive pregnancies (results in S.J.R. units)

Date	*Period*	*Mother (units)*	*Cord (units)*
7/14/57	Delivery	54.9	9.8
7/17/57	3 days post partum	32.4	
1/27/58	12 weeks gestation	4.4	
7/8/58	38 weeks gestation	36.6	
7/29/58	5 days post partum	18.7	
9/20/59	Delivery	36.7	11.8
2/8/60	4 months post partum	5.2	

nancy. This was observed with glutamic oxalacetic transaminase and lactic dehydrogenase. These higher activities in the mother cannot be related to necrotic maternal processes, nor have liver function changes in the later stages of pregnancy been adequately demonstrated.

The enzymes which are elevated in pregnancy and in the fetal circulation are also those known to be in high concentrations in the erythrocytes. However, excessive red cell destruction and intravascular hemolysis were not found in either the mother or the fetus and could not account for the elevated activity.[5]

In summary, the lowered cholinesterase and tributyrinase levels which appear in the maternal serum as pregnancy advances are further diminished in the cord serum.[5] The elevated transaminase and lactic dehydrogenase in the maternal serum are further increased in the cord serum. The consistent pattern of decrease in the esterases and increase in transaminase and lactic dehydrogenase suggests some underlying and unknown metabolic functions which are responsible.

Alkaline phosphatase has its own characteristic pattern in that it increases during pregnancy starting with the second trimester, reaches high levels at term, and then shows significantly lowered activity in the cord serum when compared with that of the mother at delivery. Wetstone and co-workers[17] found a similar rise in alkaline phosphatase during the third trimester of pregnancy which reached a peak during labor. These authors ruled out extrahepatic obstructive factors and related the increased alkaline phosphatase to increased bone metabolism during pregnancy.

The data of Table VI suggest some interesting speculation as to the phosphatase mechanism during pregnancy. This patient was clinically normal during her obstetric course and during the nonpregnant intervals, and seemed to show an exaggerated pattern of alkaline phosphatase changes as compared with all of the others in this study. In our present knowledge,[18] elevated alkaline phosphatase to the extent seen here is a manifestation of bone disease or the result of a hepatobiliary obstruction. This patient was appearently normal with no appearance of jaundice at any time. Nor was there any evidence of bone abnormality. Furthermore, it is remarkable that these increases occurred during 3 successive pregnancies. With the negative x-ray findings and the normal clinical course during gestation, some cause other than bone or liver disease must be sought to explain these exceptional changes. Perhaps this is an exaggerated situation of increased alkaline phosphatase generally noted in pregnancy at term, and results from the same mechanism. It is, therefore, suggestive that the markedly elevated alkaline phosphatase in this patient, and the elevations that occur at term in all pregnancies, are not the result of liver and/or bone abnormalities but rather from some unknown but normal metabolic phenomenon that occurs near term.

Summary

Serum enzyme levels were determined in mothers during the entire course of pregnancy.

Esterases (cholinesterase and tributyrinase) were decreased during pregnancy. Glutamic oxalacetic transaminase, alkaline phosphatase, and lactic dehydrogenase were increased during pregnancy.

The significance of these changes is discussed.

We wish to thank Isaac A. Ford and Marilyn S. Lapan for their technical assistance.

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Effect of 4-aminopteroylglutamic acid on midgestation in the rat

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ALVAN G. FORAKER, M.D.
GENEVIEVE A. MARINO, B.A., H.T.(ASCP)
Jacksonville, Florida

As part of a continuing study of the effect of cell-damaging agents upon the placenta, the antimetabolite 4-aminopteroylglutamic acid (Aminopterin) (4-amino-PGA) was administered to rats just prior to midgestation. The tissues were studied by special staining methods. Selective damage of embryonic elements was noted, with lesser and secondary effect upon maternal elements of the gestation.

Materials and methods

Sprague-Dawley rats with an average gestation period of 23 days were employed. Tissue from 7 pregnant rats receiving no treatment was examined as control for the first series, to be noted below. On the presumed thirteenth day of gestation the right uterine horn with attached oviduct and ovary was removed. As control for the second series, 7 pregnant rats receiving no drug were similarly subjected to excision of the right uterine horn with attached oviduct and ovary on the presumed tenth day of gestation. The rats were then allowed to proceed to term. The majority had normal deliveries from the remaining uterine horn. The rats were then sacrificed. The left uterine horn with attached oviduct and ovary was removed.

In the first treatment series, 12 rats were employed. On the presumed ninth day of gestation, 4-amino-PGA (10 mg. per kilogram of body weight) was administered intraperitoneally. On the presumed thirteenth day of gestation, the right uterine horn with attached oviduct and ovary was removed. In the second treatment series, 11 rats were employed. On the presumed ninth day of gestation, 4-amino-PGA (10 mg. per kilogram of body weight) was administered intraperitoneally. On the following day (presumed tenth day of gestation) the right uterine horn with attached oviduct and ovary was removed. Rats in both treatment series were observed past the presumed twenty-third day of gestation, when the remaining uterine horn with attached oviduct and ovary was removed.

Tissue blocks from all specimens were fixed in buffered formalin. The blocks were processed through alcohol, acetone, and xylol to paraffin. Five micron sections were stained with hematoxylin and eosin, Masson's trichrome,[4] Snook's reticulum, Verhoeff's elas-

From the Research Laboratory, Baptist Memorial Hospital.

This investigation was supported by research grants from the National Cancer Institute, National Institutes of Health, United States Public Health Service (C-3449), and the Damon Runyon Memorial Fund (DRG-478).

Presented at the Fourth International Congress on Clinical Pathology, Madrid, Spain, June 15, 1960, and at a meeting of the Sociedad Ginecologica Española, held in the Department of Obstetrics and Gynecology, University of Madrid, June 15, 1960.

tic, and periodic acid–Schiff[5] (undigested and amylase digested) techniques.

Results

In the untreated rats, the general gross and microscopic morphology (Fig. 1) of the placenta and allied structures corresponded to the standard descriptions.[1] There was much less evidence of glycogen (comparison of undigested and amylase digested periodic acid–Schiff stained sections) than we[3] had previously found in rabbit decidua. The postpartum uterine horns of the untreated rats showed a subsiding chronic inflammation with histiocytes in the endometrial stroma containing brown hemosiderin-type pigment. In all of the material of this study, elastic fibers were found only in walls of maternal arteries and veins. The elastic fiber pattern showed no response to 4-amino-PGA therapy and will not be further mentioned.

The majority of the treated animals developed diarrhea, epistaxis, and lethargy. A few had demonstrable intestinal ulcerations. At laparotomy the tissues appeared darker and more friable. In the first treatment series, where 4 days elapsed between drug administration and laparotomy, the gestations were observed to be somewhat smaller than in the control animals. No gross evidence of embryos could be discerned. Microscopically (Fig. 2) the findings consisted principally of disintegration and destruction of virtually all embryonic elements, with necrosis and acute inflammatory reaction in the placental labyrinth. This was associated with fragmentation of reticulum fibers in the labyrinth. Deeper layers of decidua, adjacent endometrium between gestations, myometrium, oviduct, and ovary showed no change. In tissues removed at the the twenty-third day of gestation extensive areas of necrosis and inflammation occupied the sites from which abortion had occurred. In some areas inflammation had spread through the myometrium into adjacent fat.

In the second treatment series, where one day elapsed between therapy and lapa-

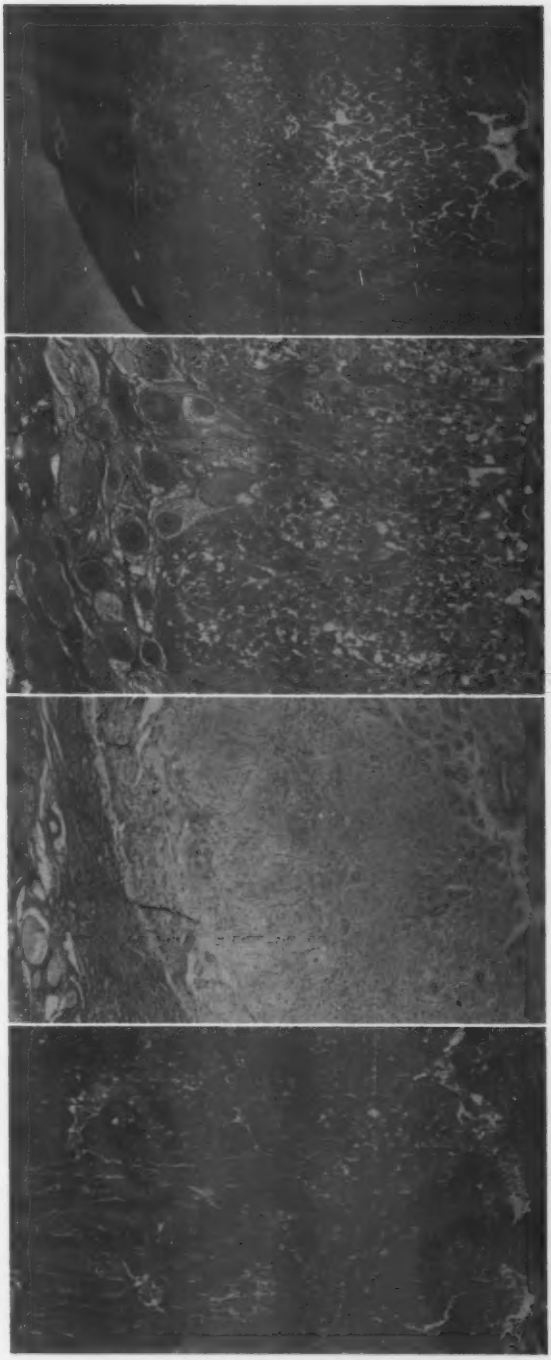

Fig. 1. Normal gestation of rat (presumed thirteenth day of gestation). *A*, Low power view showing myometrium decidua basalis, giant cells, placental labyrinth, and vascular spanchnopleur. (Masson's trichrome; ×65.) *B*, Detail from same section showing giant cells at left and placental labyrinth at right. (Masson's trichrome; ×260.) *C*, Considerable reticulum in myometrium at left, with outlining of vessels in decidua and placental labyrinth. (Reticulum; ×65.) *D*, Dark staining of cytoplasm in decidua near junction with placental labyrinth is indicative of glycogen. (Periodic acid–Schiff undigested, hematoxylin counterstain; ×260.)

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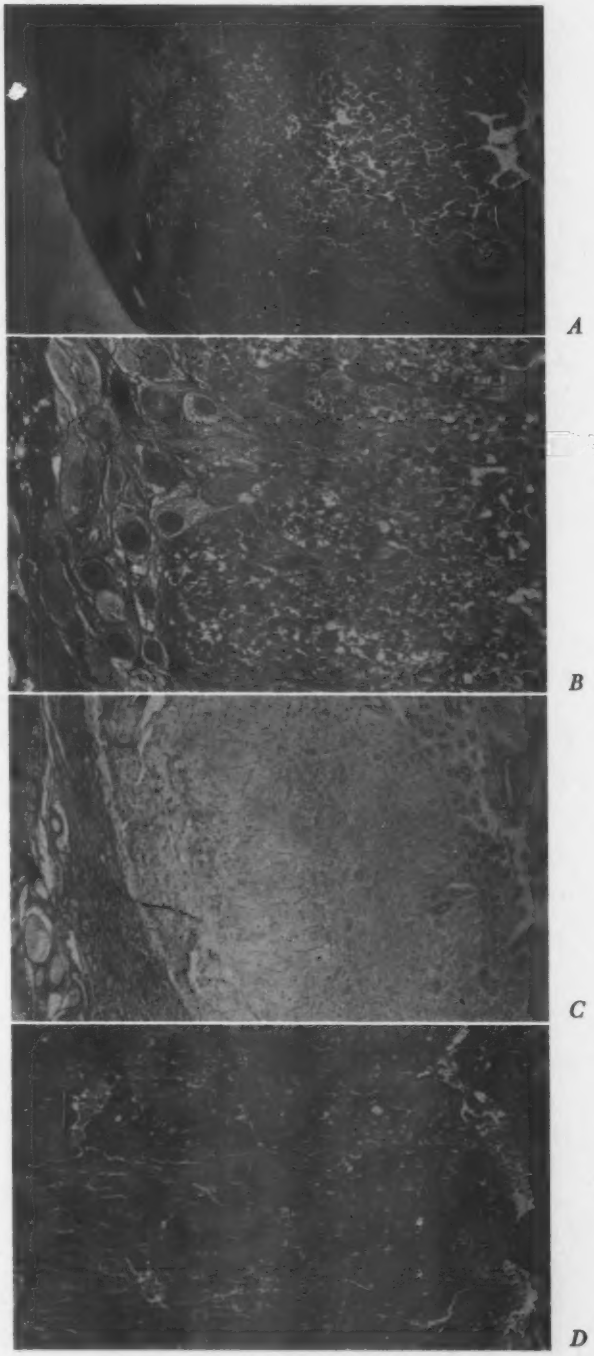

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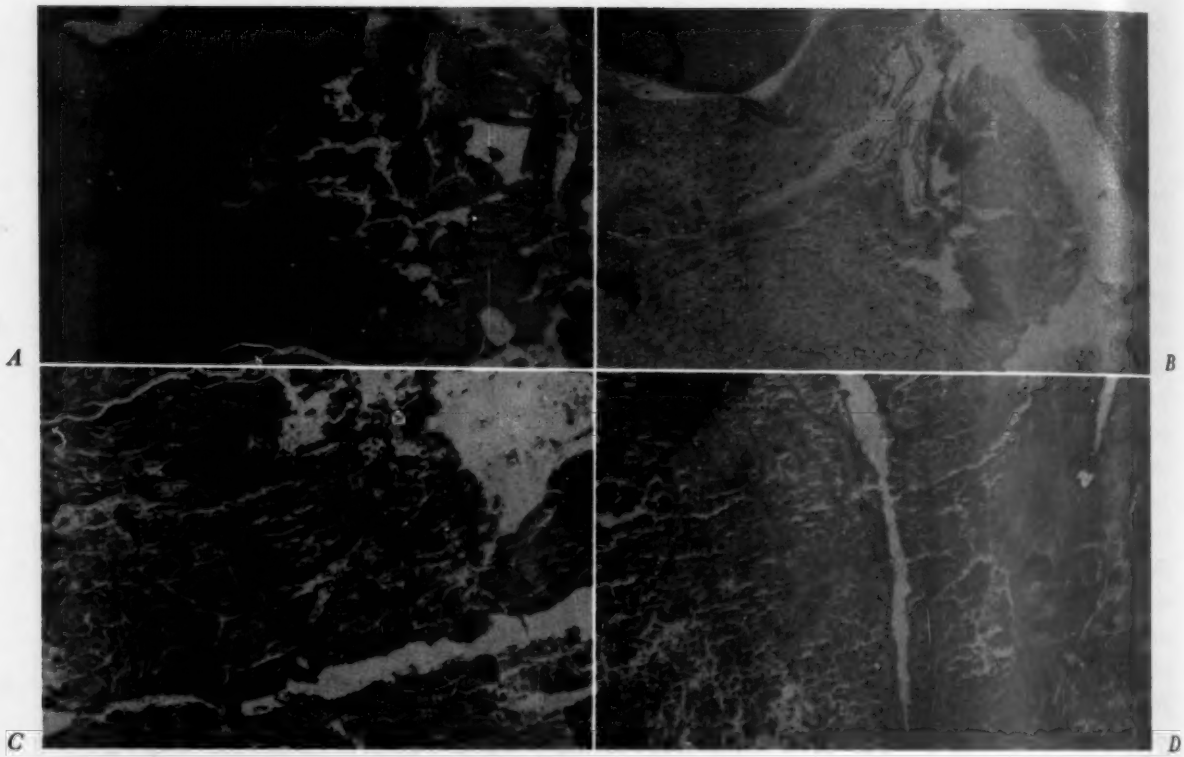


Fig. 2. Thirteenth day gestation of rat administered 10 mg. per kilogram of 4-amino-PGA on ninth day of gestation. *A,* Necrosis of fetal elements in right center, with comparatively less involvement of decidua in left center. Glandular epithelium in lower right and at bottom is from adjacent endometrium. (Hematoxylin and eosin; ×65.) *B,* Fragmentation of reticulum in region of necrosis, with comparatively less disturbance in decidua. (Reticulum; ×65.) *C,* Comparative sparing of decidua at left and lower portions of field, with disintegration of fetal elements above and at right. (Masson's trichrome; ×260.) *D,* Absence of glycogen staining in decidua at left. Disintegrating fetal elements at right. (Periodic acid–Schiff, hematoxylin counterstain; ×260.)

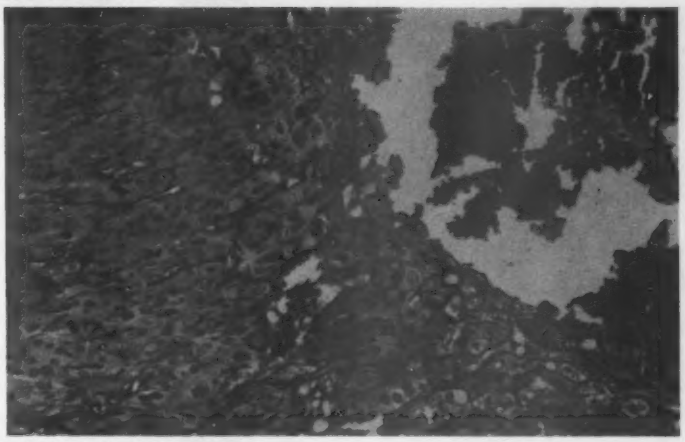
rotomy, the gestations showed less change in general size, but no embryos could be discerned grossly. Microscopically, remnants of viable embryonic tissue could be found rarely (Fig. 3). Foci of necrosis and inflammation in the placental labyrinth were smaller than those in the first treatment series. Again, deeper layers of decidua, adjacent endometrium between gestations, myometrium, oviduct, and ovary showed no change. In tissues removed at the presumed twenty-third day of gestation (Fig. 4), the pattern was identical with that of the first treatment series.

Three rats in the first treatment series and 4 in the second series were discovered not to be pregnant at laparotomy. The uteri, oviducts, and ovaries of these animals showed no gross or microscopic change attributable to 4-amino-PGA therapy.

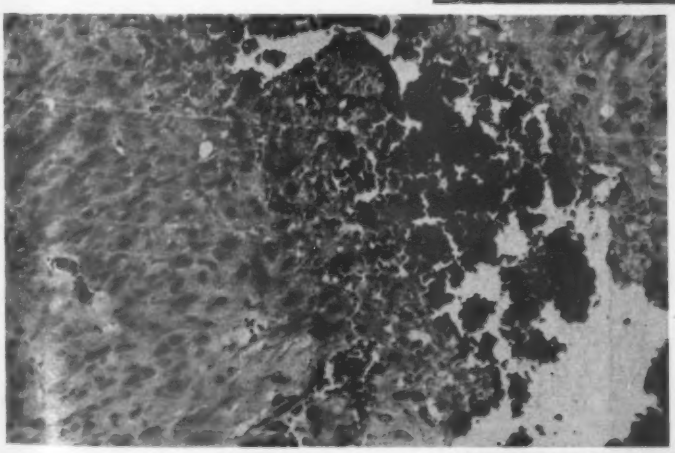
Comment

Our original interest in this field was in utilization of the placenta as a general test organ for studies in rapid cell growth in normal and abnormal states. In 1954[2] we compared the findings of a battery of histochemical techniques in the normal rabbit placenta. Sites of succinic dehydrogenase activity were localized in the rabbit placenta in midgestation. There was little correlation between sites of this enzyme group's activity and the localization of alkaline phosphatase, lipid, or glycogen. Subsequently[3] the left uterine horns of rabbits were exposed to a single dose of 1,200 r

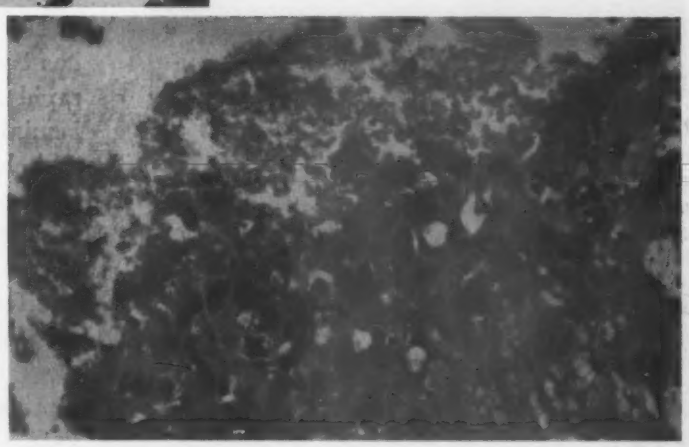
Fig. 3. Tenth day of gestation of rat administered 10 mg. per kilogram of 4-amino-PGA on ninth day.
A, Necrosis of fetal element in center with comparative sparing of maternal element. Area of necrosis is smaller than in Fig. 2. (Hematoxylin and eosin; ×65.)



B, Preservation of reticulum in decidua, with fragmentation in region of necrosis. (Reticulum; ×260.)



C, Disintegration and necrosis of fetal elements at right. (Masson's trichrome; ×260.)



D, Detail of same process as in *C*. Note pyknotic darkly staining nuclei. (Periodic acid–Schiff, undigested, hematoxylin counterstain; ×650.)

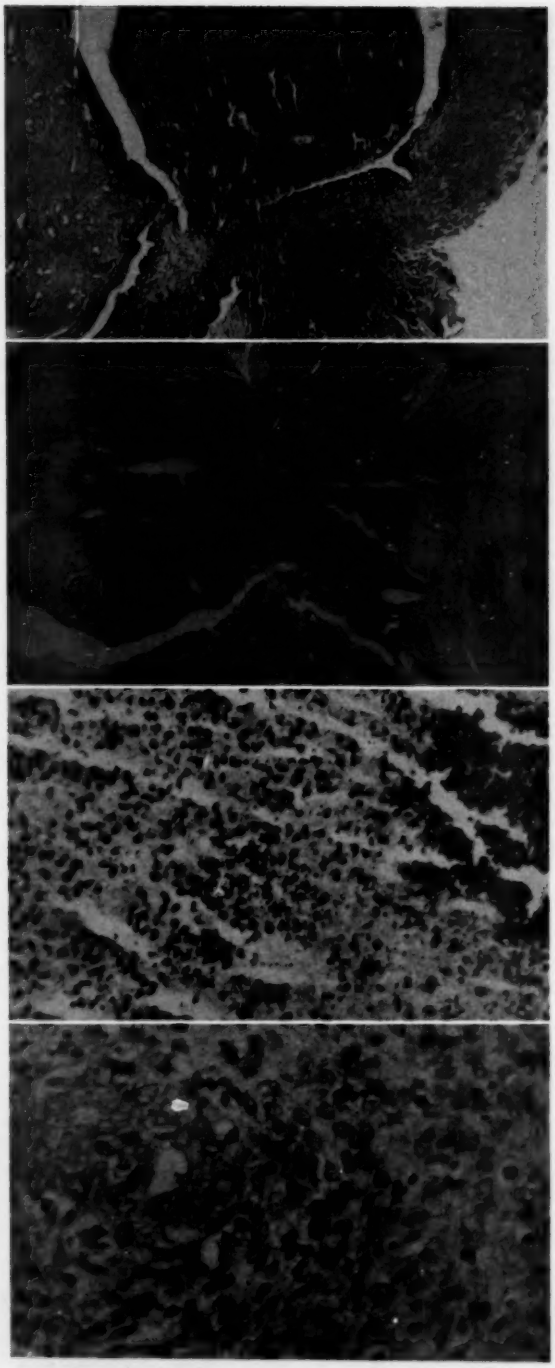


Fig. 4. Twenty-third day of gestation of rat administered 10 mg. per kilogram of 4-amino-PGA on ninth day. *A*, Mass of necrotic and disintegrating cellular debris fills uterine lumen. (Masson's trichrome; ×65.) *B*, Disintegration of reticulin in necrotic material, with reservation in adjacent myometrium. (Reticulum; ×64.) *C*, Necrotic decidua at left, with cellular debris at right. (Hematoxylin and eosin; ×260.) *D*, Endometrial gland and stroma. Dark cell in center contains brown pigment, probably hemosiderin. (Periodic acid–Schiff, digested, hematoxylin counterstain; ×650.)

KVP radiation on the ninth day of gestation. Five days later placental tissue from both uterine horns was studied by histochemical techniques. Tissue from the right uterine horn showed no evidence of radiation damage. Evidence of radiation damage in the left uterine horn was concentrated in a proportion of syncytial cells and in perisyncytial decidual cells. These showed nuclear pyknosis, cell disintegration, and necrosis. Cytochemically, this cellular damage was reflected by diminution in dehydrogenase activity, appearance of lipid granules, and nonglycogen periodic acid–Schiff positive material. These reactions appeared to be nonspecific manifestations of cellular damage, not peculiar to irradiation effect.

The major findings of the current study are in essential agreement with those of Thiersch and Philips[5] who reported that 4-amino-PGA was lethal to the early embryo of mice and rats. Fetal death was observed with doses which caused no significant signs of intoxication of mothers except temporary depletion of bone marrow. In 1952, Thiersch[6] reported that the administration of oral doses of 6 to 12 mg. 4-amino-PGA to humans induced fetal death in the first trimester of pregnancy followed by spontaneous delivery of the products of conception in 10 of 12 patients treated. Only a slight and transitory depression of hemoglobin and white blood counts was found in the mothers. In 1956 Thiersch[7] found that 9 of 12 antimetabolites studied affected rat embryos adversely.

The therapeutic use of antimetabolites has been based upon their interference with rapid and abnormal cellular growth in leukemias and malignant tumors. It seems probable that their effect on the embryos is analogous. It is our present impression that antimetabolites do not have a specific lethal effect on embryonic tissue as such, but interfere with rapid cellular growth and metabolism in general. Since embryonic tissue *is* rapidly growing, it is markedly susceptible to chemical agents such as 4-amino-PGA.

Summary

The effect of 4-aminopteroylglutamic acid (Aminopterin) on midgestational pregnancy in the rat has been studied. Four days after administration of 4-amino-PGA (10 mg. per kilogram of body weight) on the ninth day of gestation, there was disintegration and necrosis of fetal elements and immediately adjacent placental labyrinth. One day after administration of 4-amino-PGA (10 mg. per kilogram) on the ninth day of gestation, remnants of embryonic elements remained, with foci of necrosis in the adjacent placental labyrinth. Gestation in the remaining uterine horns was interrupted, with residual inflammation and necrosis at the placental site. These findings are believed to be general nonspecific effects upon the rapidly growing embryonic tissue.

Appreciation is expressed to the Research Division, American Cyanamid Company, Pearl River, New York, for supplying the 4-aminopteroylglutamic acid (Aminopterin) used in this investigation.

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Effect of a histaminase inhibitor (aminoguanidine sulfate) on pregnant and nonpregnant rats

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DESPITE constant investigation, the cause of toxemia of pregnancy (pre-eclampsia) is still not determined. So many theories have been propounded that pre-eclampsia has been referred to as the "disease of theories." Among the concepts of etiology is the suggested correlation of low histaminase levels and the state of pre-eclampsia.

Basic concepts

There is a physiologic relationship between histaminase levels and the amount of free histamine released. Increasing circulating histamine causes arteriolar constriction and capillary dilatation, resulting in increased interendothelial spaces with the escape of fluid into the tissue spaces. The arteriolar constriction in the renal circulation causes diminished clearance. Theobald[1] concluded that the marked increase of histaminase during normal pregnancy was essential to the control of free histamine. He noted that the enzyme was elaborated by the decidua and was diminished in the presence of toxemia of pregnancy. Clark and Tankel[2] state that the histaminase is derived from the placenta and increases in the plasma of pregnant women often to levels of 1,000 to 2,000 times the amount in the nonpregnant state. Ahlmark[3] concurred with this and found that the peak concentration of histaminase was between the twenty-seventh and the thirtieth week of gestation. Hofbauer,[4] in a paper concerned with experimental studies in toxemia of pregnancy, concluded that the increased amounts of free histamine may be responsible for the pre-eclamptic syndrome. Kapeller-Adler[5] suggested that histamine intoxication may manifest itself by hyperemesis gravidarum, pre-eclampsia, or eclampsia. Yamada[6] firmly states that eclampsia arises from allergic reactions. His opinion is based on tissue changes resulting from allergic sensitization with the serum of eclamptic women in rabbits. The pathologic changes failed to occur following animal sensitization with the serum of nontoxemic pregnant women. In pursuit of this concept, the relationship of histaminase levels to the occurrence of toxemic signs in pregnant rats was studied.

Method

Aminoguanidine sulfate is an efficient histaminase inhibitor. Roberts[7] used this drug to inhibit the histaminase in pregnant rats. He found that when the histaminase value was depressed 50 per cent or more, disturbance of the pregnant animal occurred, resulting in maternal and fetal death. Similar dosage of aminoguanidine sulfate in nonpregnant rats caused no untoward reaction. He concluded that histaminase protects the mother against the noxious effects of histamine. Histologic evidence was not submitted in support of this relationship.

The effect of the administration of amino-

From the Obstetrical and Laboratory Services of the Newark Beth Israel Hospital.

Aided by a grant from the Research Foundation of the Newark Beth Israel Hospital.

guanidine sulfate was studied in pregnant and nonpregnant rats. For the purpose of controlled study, two groups of animals were established; the pregnant and the nonpregnant. In each group 4 subgroups were studied: (A) those fed on water and receiving no medication; (B) those fed on normal saline and receiving no medication; (C) those fed on water and receiving aminoguanidine sulfate; and (D) those fed on normal saline and receiving aminoguanidine sulfate.

In accordance with the pattern established by Roberts,[7] planning to suppress 50 per cent or more of maternal placental histaminase, 50 mg. of aminoguanidine sulfate, dissolved in distilled water to a 25 per cent concentration was administered subcutaneously daily for 12 days.

Daily blood pressure and weight were taken on each animal in all groups. The blood pressure was taken by a photoelectric cell device,* detecting light shining through the front paw of the animal after constriction with a small blood pressure cuff.

After 12 days, 2 animals in each of the 4 subgroups of the nonpregnant rats were sacrificed; in the pregnant animals, 4 were sacrificed in subgroup A, 3 in subgroup B, 3 in subgroup C, and 5 in subgroup D. Histaminase determinations were done on 2 placentas in A, 2 in B, 2 in C, and 5 in D. In all of the animals sacrificed, tissue studies of the liver and kidney were made following autopsy.

Results

In the nonpregnant group, 23 animals were studied, 5 in group A, 6 in groups B, C, and D. No elevation of blood pressure occurred in the nonpregnant animals. Postmortem examination of 2 animals in each group revealed no significant histologic changes in the liver or kidneys.

Twenty pregnant animals were studied; 5 in each subgroup. All the animals not receiving aminoguanidine sulfate had no significant elevation of blood pressure or any significant histologic changes in the liver and kidneys. Of the water-fed animals receiving aminoguanidine sulfate, appreciable blood pressure elevation occurred in 75 per cent of the animals studied. Postmortem examination in this group showed no pathologic condition of the liver or kidney despite clinic hypertension. Saline-fed animals receiving aminoguanidine sulfate all showed hypertension and significant pathologic changes in the liver and kidneys.

Histaminase determinations were made on the placentas by the method of Kapeller-Adler,[8] without attempting to separate the maternal from the fetal components. The placentas from the normal water-fed pregnant rats showed 1.7 to 8.9 P.U.* (average 5.3 P.U.). The placentas from the saline-fed pregnant animals showed 0.0 to 22.8 P.U. (average 11.4 P.U.). The placentas of the pregnant animals treated with aminoguanidine sulfate and water fed revealed 6.2 to 23.2 P.U. (average 14.7 P.U.), and the placentas of pregnant rats treated with aminoguanidine sulfate and saline fed, showed 2.5 to 44.7 P.U. (average 27.5 P.U.).

Variations in weight gain showed no relationship to administration of aminoguanidine sulfate. Saline-fed pregnant animals, however, gained 10 per cent more weight than the water-fed animals.

Comment

The feeding of both pregnant and nonpregnant animals on saline alone caused increased body weight but no pathologic changes, or increase in the blood pressure. The increased body weight might be interpreted as a tendency to accumulate extracellular fluid.

Administration of aminoguanidine sulfate was expected to decrease the histaminase levels of the placentas, but this did not occur. Actually an increase in the histaminase level was found, especially in the saline-fed pregnant animals. Increases in blood pressure oc-

*Photoelectric tensometer, Metro Industries, Long Island City, New York.

*Denotes permanganate units per gram of tissue.

curred in both groups of pregnant animals receiving aminoguanidine sulfate (water fed and saline fed). Pathologic changes in the liver and kidneys occurred only in the saline-fed pregnant rats which also received aminoguanidine sulfate.

The correlation of diminished histaminase with pre-eclampsia-like signs was not found in this experiment. Contrary to Roberts'[7] results, the administration of aminoguanidine sulfate did not decrease the histaminase levels. However, the administration of aminoguanidine sulfate to pregnant animals caused signs related to pre-eclampsia-hypertension and liver and kidney changes. These effects were not noted in nonpregnant animals receiving this medication.

Previous studies reported decreased concentration of placental and/or blood histaminase content in experimental toxemia as compared with levels determined in normal pregnancy. It was concluded that this diminished enzyme level resulted in an increased amount of free histamine, the action of which was therefore related to the initiation of toxemia. The results herein reported showed on the contrary a marked increase of histaminase concentration in the placentas of those in the groups associated with clinical and pathologic evidence of toxemia. It is conceivable that this finding represents an increased enzyme immobilization or storage and may nevertheless be accompanied by an increased circulatory free histamine level. In this event one may, therefore, speculate as to the possible relationship of increased free histamine to toxemia of pregnancy induced by enzyme suppression rather than enzyme defect.

Summary

1. The concept of inhibition of histaminase levels in pregnant animals by aminoguanidine sulfate was tested.

2. The correlation of diminished histaminase level with symptoms and signs of pre-eclampsia was studied.

3. In this series, aminoguanidine sulfate administered to nonpregnant animals caused no significant clinical or pathologic changes. When it was administered to pregnant animals, histaminase levels rose, rather than fell, but significant pre-eclamptic changes in blood pressure, liver and kidneys occurred.

4. Saline-fed pregnant animals showed a 10 per cent greater gain of weight than did water-fed animals.

5. An explanation of the occurrence of the signs of pre-eclampsia with aminoguanidine sulfate despite rising histaminase levels is offered. Further testing of these concepts is planned.

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Investigations on the vascular system of the placenta

Part I. General introduction and the fetal vascular system

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SINCE the placenta consists for the most part of an intricate complex of vessels, it is obviously of fundamental importance to a correct understanding of the physiology of this organ, and the many physiological convictions that may arise in it, to obtain complete knowledge of both the fetal and the maternal vascular system.

The literature shows that, particularly in the past few years, intensive attempts have in fact been made to investigate placental morphology and physiology. The vascularization of the placenta is, however, still a subject of discussion. The descriptions and illustrations presented by many prominent investigators of the course of the capillaries in the placental villi vary widely and are in many respects even contradictory.[8, 13, 32, 39-46]

There is marked discrepancy in the views on the venous drainage of maternal blood from the intervillous spaces of the placenta. Spanner[37, 38] regards the marginal sinus as the only route of drainage of maternal blood from the intervillous space, whereas Hamilton and Boyd[18] deny even the existence of the marginal sinus. Earn and Nicholson,[15] however, support Spanner's theory, while Ramsey[25-29] believes that the venous drainage of maternal blood takes place both via uteroplacental veins originating from the marginal sinus (referred to by Ramsey[27, 28] as marginal lakes) and via uteroplacental veins extending from the intervillous space underneath the entire basal plane of the placenta.

We have investigated the vascular system of the placenta with the aid of the corrosion technique. Among other aids, we used a special plastic solution (polymethylmethacrylate).

Method

Our material consisted of 65 normal human placentas obtained during the fortieth week of pregnancy. The procedure was as follows: Immediately after parturition, as much of the blood as possible is drained from the placenta via the umbilical cord. As soon as the placenta has been expelled, it is drained still further by careful compression.

Within 1 to 2 hours of expulsion the placenta is washed out to remove the remaining blood. For this purpose a polyethylene catheter is introduced into both the umbilical vein and an umbilical artery. It is possible to fill the entire arterial system via one umbilical artery, as the two umbilical arteries anastomose at the site of insertion of the cord into the placenta.

Washing out is done with an aqueous solution of 3.8 per cent sodium citrate, via the umbilical artery, under a pressure of 90 cm.

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H_2O, i.e., roughly equal to the physiological pressure normally prevalent in the umbilical arteries (which is about 65 mm. Hg[31]). During washing out the placenta is placed in a water bath at 37° C., as this greatly facilitates the procedure. The placenta is washed out with 5 L. or sometimes with 10 L. of fluid until it is entirely free of residual blood. After washing, the placenta is carefully emptied by compression; injection of Plastoid or plastic solution can then be started.

The placenta is again placed in a water bath, this time at room temperature, to prevent the fluid injected from hardening prematurely. The water exerts an upward pressure on the placenta, which is of great importance in that the placenta is prevented in this way from exerting the full pressure of its weight on the basal plane, in which case the capillaries and the choriodecidual vessels would not be completely filled at the sites exposed to pressure, where these vessels would be compressed.

A study of the gross vascular structure can be successfully made with the aid of thick, syrupy Plastoid* which polymerizes into a glass-hard mass in the incubator at 37 to 40° C. The shrinking factor is inconsiderable. The Plastoid is injected into the placenta through a polyethylene catheter with the aid of a 5 ml. record syringe, under a pressure higher than the physiological (about 200 mm. Hg, on account of the low viscosity).

Complete filling of the smaller vessels and capillaries, however, requires the use of a thinly fluid plastic solution which is subject to a minimum of shrinking on hardening.† This substance is a solution of polymethylmethacrylate in the monomeric methylmethacrylate, which can be stored for a considerable time at a low temperature. Another advantage of this thinly fluid substance is that it can be injected under a virtually physiological pressure, which is of great importance in obtaining as exact a replica of capillary structures as possible.

The prepolymer is injected with the aid of a 10 ml. record syringe which, by means of a T-piece, is connected with a manometer on which the pressure under which the plastic solution flows into the vessels can be directly read. A completely filled placenta contains 90 to 100 ml. of plastic solution. After completion of the injection the catheters are removed, and the umbilical cord is tied off with a tape.

The placenta is then turned with the maternal side upward, so that the shape of the cotyledons is not changed, and placed in a 2 per cent formaldehyde solution for 48 hours. It is subsequently stored for 3 to 4 days in a 30 per cent KOH solution in the incubator, at a temperature of 37 to 40° C. After complete corrosion by the KOH solution the placenta is carefully placed in a basin with slowly flowing water and is left for 24 hours. It is then allowed to dry in the air. After this processing the specimen is suitable for examination.

The small structures which cannot be studied with the naked eye or with the aid of a magnifying glass should be examined with a binocular microscope, to obtain magnifications up to ×40. The capillary structures can be dissected out with the aid of extremely fine needles or finely drawn glass points.

An exact study of the course of the capillaries requires the use of a microscope affording greater magnifications. In that case the capillaries should not be placed in a fluid such as Canada balsam, as this would disturb the three-dimensional proportions. Instead the capillaries under examination are placed on a dry slide and covered with a dry cover slip which is only slightly and carefully pressed on.

Results of personal observations

The following classification is used for our findings regarding the course of the vessels in the placenta: (a) the chorionic vessels, i.e., the vessels found in the chorionic plate of the placenta; (b) the vessels of the cotyledons,

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†The Synthetics Institute T.N.O. (Delft, The Netherlands) provided us with such a plastic solution in the form of 100/4/2 O.A. cp 265/20° (viscosity at 20° C. is 265 centipoises); this solution met all our requirements.

Fig. 1. General view of course of chorionic vessels.

Fig. 2. Double arterial supply to a marginal cotyledon.

arising from the chorionic vessels and constituting the vascular complex of the cotyledons; (c) the capillaries in the villi; (d) the paravascular capillary network.

a. **The chorionic vessels.** Our study of the chorionic vessels included an exhaustive investigation into the anastomoses between the two umbilical arteries at the site of insertion of the umbilical cord into the placenta. We were able to demonstrate these anastomoses in all our specimens except one; in this latter case we found only one umbilical artery. In the many types of anastomoses between the two umbilical arteries found in our specimens three main types immediately stand out, viz., anastomosis via a separate vessel, a lateral anastomosis, and anastomosis by complete conjunction of the two vessels. These types correspond to the three chief types of anastomosis described by Fournier.[16]

We found a relationship between the site

Fig. 3. Corrosion specimen of an incompletely injected cotyledon—basal plane.

Fig. 4. Gross vascular structure of a cotyledon.

of insertion of the umbilical cord into the placenta and the course and ramification of the chorionic vessels. As a result, we were able to divide the majority of placentas examined into the three groups previously indicated by Shordania.[35]

Both the umbilical arteries and the umbilical vein become vessels of the first order at the site of insertion of the cord into the placenta, and in their further course they show a dichotomous division into vessels of the second, third, and sometimes the fourth order (Fig. 1).

The chorionic arteries extend across the chorionic veins, although there are exceptions to this rule. In a large number of specimens we found that one or several venous branches of the first, second, or third order superficially crossed the corresponding arterial branches.

Descriptions of the course of the chorionic vessels found in the literature roughly corresponded to our own findings. We maintain, however, that the course of the chorionic arteries is not always quite so regular as is usually believed to be the case. In the majority of cases, moreover, the arteries and veins run a parallel course only over relatively short distances, meeting only at the point of entry into the cotyledons.

The chorionic vessels of the first, second, third, and fourth orders give rise to vessels which perforate the chorionic plate and then connect with the vascular tree of the cotyledons. These vessels which perforate the chorionic plate are referred to as perforating arteries and veins[7] or as villous vessels of the first order.[46] In this connection we noticed that in many cases one ramus of a chorionic vessel immediately enters a cotyledon while the other ramus continues and subsequently divides into chorionic vessels of a higher order.[10, 11]

In only 2 of the 65 specimens did we find a single marginal cotyledon with a duplicate arterial supply (Fig. 2); this can be regarded as a rather rare finding, and consequently we disagree with Romney and Reid,[32] who maintain that the majority of the peripheral cotyledons have a double arterial supply.

Apart from the anastomosis between the 2 umbilical arteries we were unable to demonstrate any anastomoses either between chorionic arteries or between chorionic veins; neither did we find any arteriovenous anastomoses. Boussin and Brindeau,[7] Fraser,[17] Albano,[1] and Fournier,[16] did find such anastomoses. This may be due to the fact that they used the less satisfactory radiological technique of examination.

Our specimens frequently showed small vessels running in the plane of the chorionic

Fig. 5. Corrosion preparation of a completely injected cotyledon—section.

plate; in our opinion these vessels are indubitably involved in the nutrition of the chorionic plate. Crawford[11] denied the existence of these vessels.

In none of our specimens was the existence of vasa vasorum demonstrable. Wilkin[46] and Laux and associates[22] claim to have found vasa vasorum.

b. The vessels of the cotyledons. On inspection of a specimen injected with a plastic solution and submitted to corrosion, and with inspection confined to the maternal side (where the placenta is fixed in the decidua), we found that the placenta is divided into a number of clearly defined, separate lobes known as cotyledons. In our investigation of the vascular course and pattern in the cotyledon we used two types of specimens, viz., cotyledons completely injected before corrosion and cotyledons incompletely injected. In the latter case the placenta was injected with Plastoid, which does not enter the smallest vessels, and in the former case we used polymethylmethacrylate, which completely fills the capillaries.

The incompletely injected and corroded cotyledon shows a loose structure; it is more or less hollow, and the basal plane shows an unmistakable opening around which the terminations of the villous vessels of the third order are arranged. These cotyledons are eminently suitable for a study of the grosser vascular structures (Fig. 3).

Fig. 6. Corrosion preparation of a completely injected cotyledon. Basal plane.

Fig. 7. A choriodecidual vessel. (Hematoxylin and eosin. Original magnification ×49.6.)

Our investigation showed that each cotyledon is supplied with blood by one (in exceptional cases, two) villous artery of the first order and is drained by one or sometimes two villous veins of the first order. These villous vessels of the first order arise from the chorionic vessels, as described in the previous section. The average diameter of the artery is 1.5 mm., and that of the veins is 2 mm. The average length is 5 to 10 mm., although this was exceeded in some cases. This villous vascular trunk of the first order subsequently forms a varying number of vessels (as a rule 4 to 8) with a horizontal course, i.e., parallel to the chorionic plate. Following the example of Wilkin,[46]

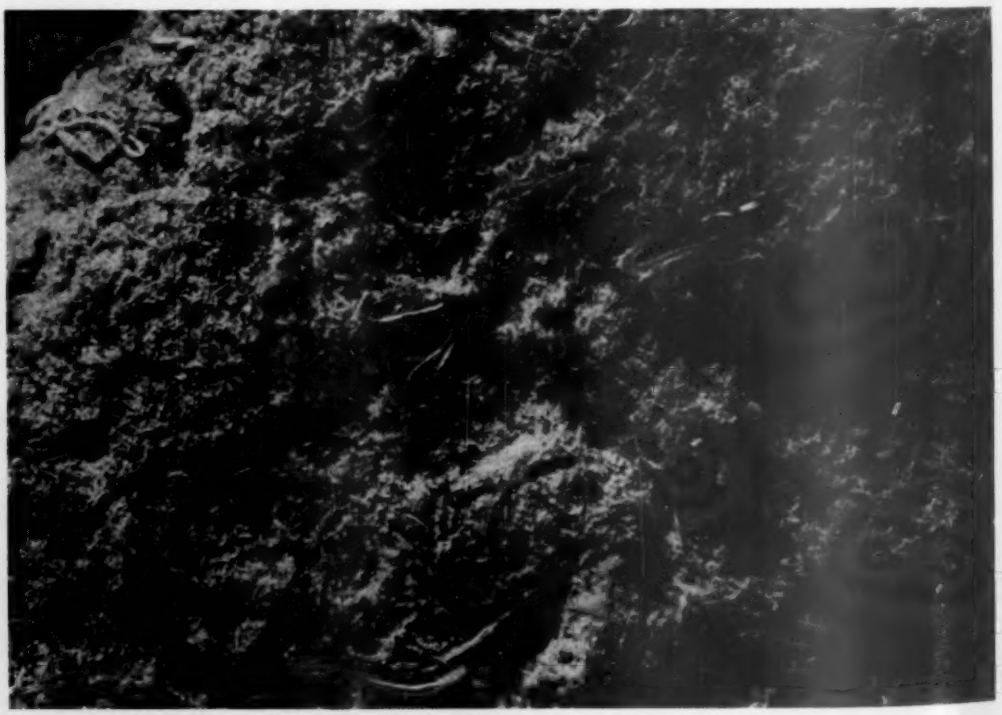

Fig. 8. Basal plane of a cotyledon with choriodecidual vessels. (Original magnification ×3.7.)

we refer to these vessels as villous vessels of the second order. These vessels, with an average diameter of 1 mm., run a horizontal course over a distance which varies with the size of the cotyledon and subsequently curve in the direction of the basal plate; at this level they are called villous vessels of the third order. However, there are also vessels extending to the basal plate from anywhere in the horizontal part of the villous vessel of the second order. These vessels number about 29 to 60 per cotyledon; they have a diameter of 0.1 to 0.6 mm. and a length of 15 to 25 mm. (Fig. 4).

The completely injected and corroded cotyledon shows a somewhat different aspect. Its structure is firmer; it has no central cavity, and there is no central hiatus at its base (Figs. 5 and 6). A checkup on microscopic sections showed that all vessels and capillaries in such cotyledons are completely filled, and the findings therefore correspond to reality. The arrangement of villous vessels of the third order in these cotyledons was found to be different from that in incompletely injected corroded cotyledons. In the latter, terminations of the villous vessels of the third order (also called choriodecidual vessels because they are implanted in the basal plate, Fig. 7) are arranged in a corona around a central hiatus (Fig. 3). In the completely injected corroded cotyledon the terminations of these vessels, which project as loops underneath the basal plane of the cotyledon (Fig. 8), occur throughout the area of the basal plane, i.e., also in the central part of this plane although this was not observed by Wilkin.[46] Wilkin seems to have based his report on incompletely injected corroded cotyledons, in which he found the terminations of the villous vessels arranged in a corona *(couronne d'implantation)*. The difference between the two types of cotyledon is shown in Fig. 9. In the incompletely injected cotyledon, the villous vessels of the third order tend more markedly than normal to a centrad curvature of their terminations, owing to insufficient filling of the cotyledon. As a result, the peripheral vessels assume a position at a

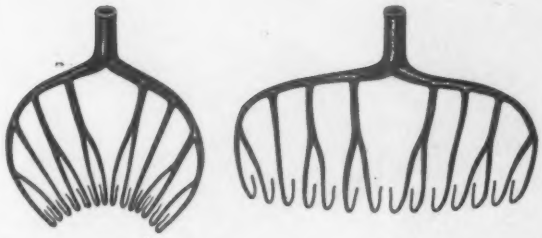

Fig. 9. Diagram of course of villous vessels in corrosion preparation of an incompletely (left) and a completely injected (right) cotyledon.

greater depth beneath the basal plate than that of the more central vessels, and the corona around the central hiatus is formed. This disappears when the cotyledon is more severely "stretched," the pattern of a completely injected corroded cotyledon then appearing. In this case the central villous vessels of the third order also reach the basal plane and contribute to the fixation of the placenta in the uterine wall.

In these cotyledons we saw clearly that only the terminations of the villous vessels of the third order ran a retrograde course in the direction of the chorionic plate. In our opinion Spanner[36-38] is incorrect in presuming that the branches of the vascular trunk themselves take a retrograde course (chandelier pattern).

We observed a difference in structure and design between the peripheral and the central part of the cotyledon. In the peripheral part, the large vessels and their branches are less precisely bundled than in the central part of the cotyledon. In the discussion of the capillaries it will be shown that these areas are also characterized by difference in capillary density and, in a sense, in capillary structure.

In exceptional cases, a large cotyledon may be composed of two or three smaller cotyledons; Crawford's[12] view that each cotyledon can be divided into a large number of subcotyledons is incorrect.

A more or less spiral course of the villous vessels of the first order was seen in a large part of the material. As a rule (but not always) the artery wound round the vein in these cases, but the vein also was often found to have 1 or 2 convolutions. This spiral

Fig. 10. Terminal artery and vein with villous capillaries at the periphery of a cotyledon. (Original magnification ×102.)

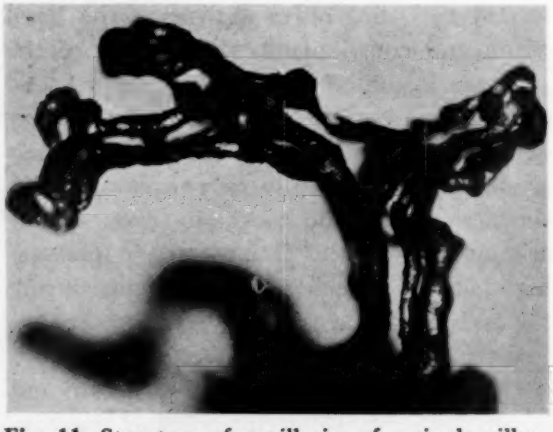

Fig. 11. Structure of capillaries of a single villus. (Original magnification ×317.5.)

pattern is not always distinct, and no special significance can be attached to it as yet.

Leaving the paravascular capillary network aside, no arterial, venous, or arteriovenous anastomoses are found in the cotyledon. Nor are there any anastomoses between adjacent cotyledons. Our findings contradict the theory preposed by Stieve[39-45] that villous vessels and capillaries constitute a vascular network (*Gefässraumgitter*). They also reveal the incorrectness of the supposition of Danesino[14] and Lemtis[23] that arteriovenous anastomoses exist. In our specimens we failed to find the constrictions in the larger villous vessels which have been described by Spanner,[37, 38] Danesino,[14] Wilkin,[46] and Mayer.[24]

c. The capillaries in the villi. The small villous vessels which arise from the larger branches of the villous vessels of the third order traverse the cotyledon in both a horizontal and a vertical direction. Throughout the length of these vessels, they give rise to the preterminal and terminal vessels. The last-mentioned vessels, which are of varying length, give rise to the numerous capillaries which constitute the typical capillary structure in the villi (Fig. 10).

Three types of villous capillary structures were found, viz., (a) simple villous capillary structures; (b) composite villous capillary structures; and (c) the villous capillary structure of the paravascular capillary network. The last-mentioned villous capillary structure—with its different structure and origin—will be discussed in the section on the paravascular capillary system.

We succeeded in demonstrating the entire capillary bed in the separate villi by the corrosion technique. Fig. 11 shows the complete capillary structure of a single villus. Fig. 12 presents a semischematic drawing of the capillary structure as it exists in a single villus.

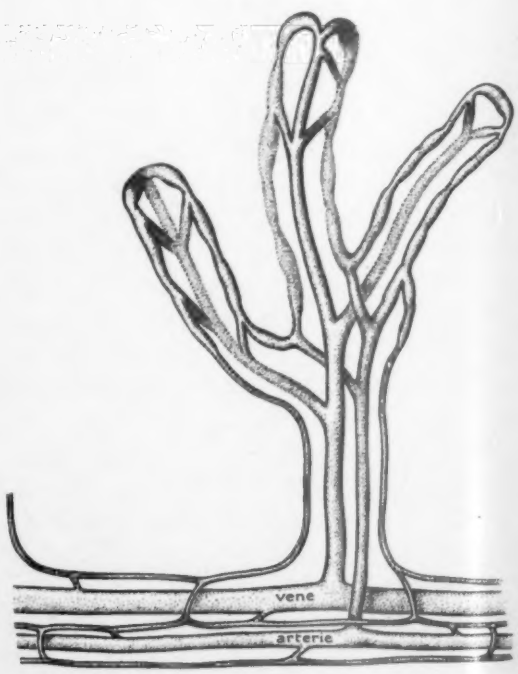

Fig. 12. Semidiagrammatic representation of the course of capillaries in a single villus.

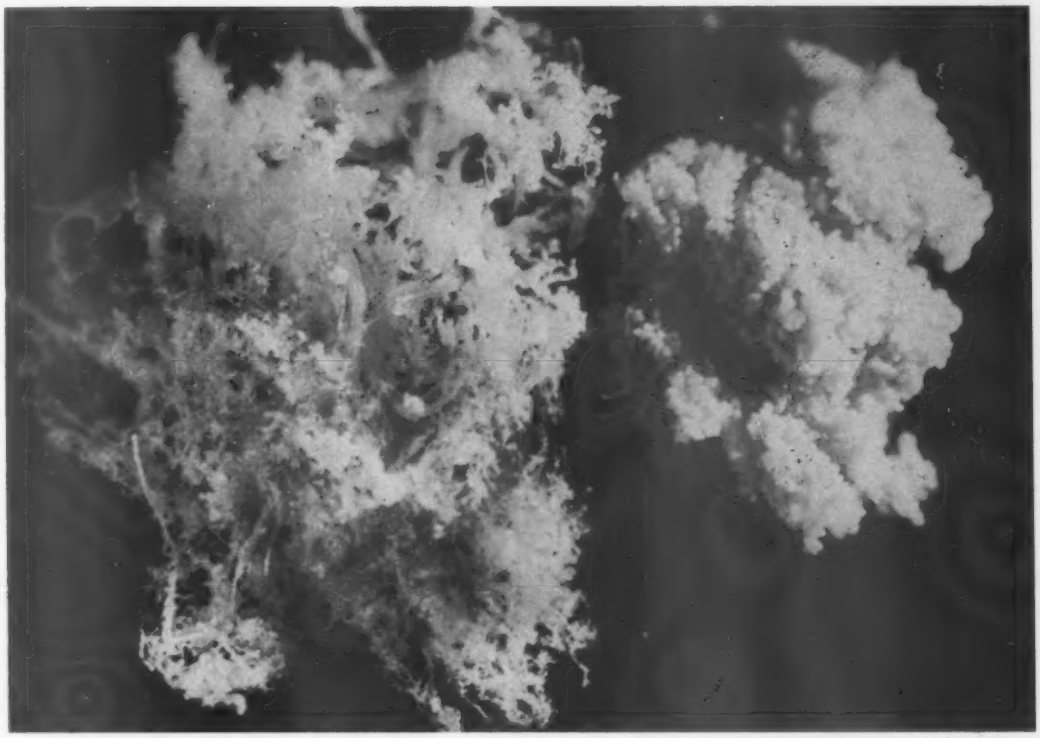

Fig. 13. Difference in density between capillaries at the periphery (left) and at the center (right) of a cotyledon. (Original magnification ×18.6.)

The composite villous capillary structure should be pictured as a simple villous capillary structure, the separate excrescences of which have grown out to become further simple villous capillary structures.

The structure of both a simple and a composite villous capillary pattern is always dependent on an independent arterial and a venous capillary which rise from a terminal vessel; also involved are one or two capillaries of the paravascular capillary network. Bøe[8] erroneously believed that the small and medium simple villous capillary structures receive blood exclusively via capillaries of the paravascular capillary network.

In the central and basal parts, as well as in the subchorionic part of the cotyledon, the capillaries of both the simple and composite villous capillary structures show sinusoid dilatations (Fig. 11). We believe that these dilatations cause the bulging in the villi which has been described by Hörmann.[20] At these bulging sites the fetal capillary comes very close to a thinned layer of syncytiotrophoblast, the maternal blood being separated from the fetal blood only by this layer of syncytium and the endothelial layer of the fetal capillary.[47]

The capillaries within a single villus anastomose only via short transverse connecting parts. There are no anastomoses between the capillaries of adjacent villi. This contradicts Stieve's view[39-45] that the capillaries of all villi constitute one network.

Not only are the capillaries in the villi unusually wide but they are also strikingly short. These short and wide capillaries ensure that, on the one hand, the fetal blood passes quickly through the placenta (having to travel only a short route) while, on the other hand, this blood is given ample opportunity for exchange with the maternal blood, the wide capillaries causing deceleration of flow. Another advantage of these wide and short capillaries is that the difference in pressure between the efferent and the afferent blood flow is small. The fetal blood meets little resistance in the capillaries, and the decrease in blood pressure

Fig. 14. Paravascular capillary network. (Original magnification ×90.)

from the umbilical artery to the umbilical vein consequently does not exceed 50 per cent. The blood pressure in the large capillary bed of the human organism, however, decreases by more than 98 per cent.[33]

The maximal capillary density is found not only in the basal but also in the central part of the cotyledon; in other words, the larger part of the cotyledon has a dense capillary structure. Only its subchorionic part (about 4 to 8 mm. thick, decreasing in a lateral direction to an average of 2 to 5 mm.) has a less dense structure (Fig. 13). We noted, however, that the basic pattern of the separate villous capillary structures was always constant in both regions (a fact pointed out by neither Romney and Reid[32] nor Wilkin[46]). Differences are found chiefly

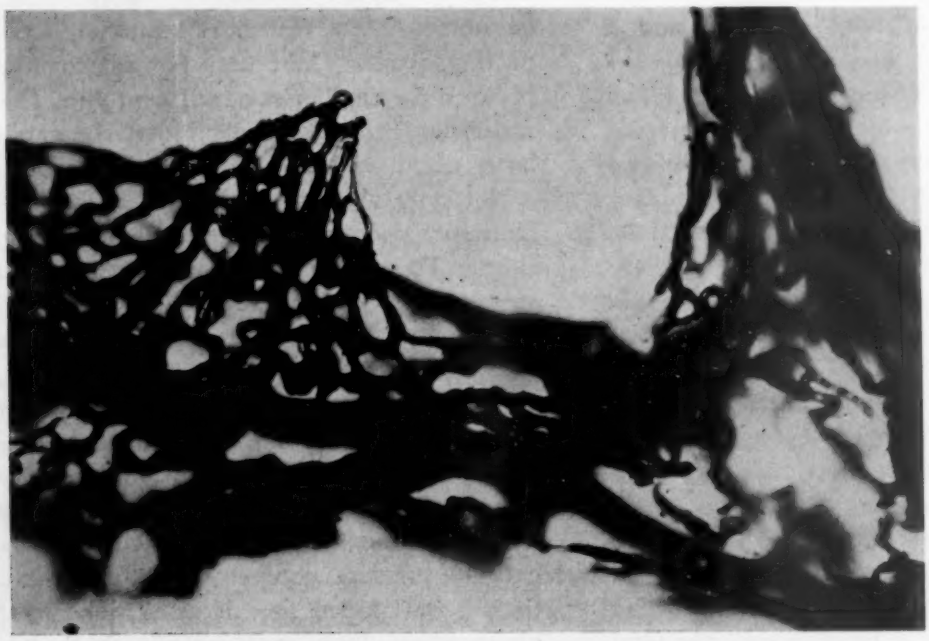

Fig. 15. Villous structures of the paravascular capillary system. (Original magnification ×124.)

in length and in the absence or presence of rolled patterns in the separate villous capillary structures, as also in the diameter of the constituent capillaries.[4]

The higher density of capillaries in the central and basal part of the cotyledon suggests that the circulation of maternal blood of the intervillous space is more intensive in this region than in the subchorionic part, where the capillaries are less densely placed.

d. The paravascular capillary network. The paravascular capillary system is a network of numerous anastomosing capillaries with a diameter smaller than that of the actual villous capillaries. This system shows its widest spread around the small branches which give rise to the terminal vessels (Fig. 14).

Since our findings show that this network has as many connections with the venous as with the arterial vascular system, we believe that it cannot be regarded as an exclusively arteriovascular network as suggested by Bøe.[8]

The paravascular capillary system invariably proved to contribute to the formation or composition of capillary structures in the villi proper which, moreover, communicated via capillaries of this paravascular network (Fig. 12).

Certain reticular villous structures were found, moreover, which were exclusively formed by capillaries of the paravascular capillary system. These capillary villous structures were located chiefly along the vessels around which the paravascular capillary network is most extensive (Fig. 15).

The paravascular capillary network is very extensive around the small branches in the subchorionic part of the cotyledon (more so than around the branches in the central and basal part). It is consequently in the subchorionic part that the purest reticular patterns and typical capillary villous structures of the paravascular capillary network are found.

Although the capillary system in the villi themselves and the paravascular capillary system communicate in numerous places, we believe that these two capillary systems nevertheless have separate functions.

The capillary structures of the paravascular capillary system are generally less superficially localized in the stroma than the villous capillaries localized in the villi. This, however, forms no objection to ascribing a function in the exchange between maternal and fetal blood to the paravascular capillary system. The fetal stroma of the placenta is known to receive its nutrition from the maternal blood which circulates around this system of tissue,[48] so that nutritional products must be presumed to be able to reach these capillaries from the maternal blood via the placental stroma surrounding the vessels. The paravascular capillary system has its widest spread in the subchorionic peripheral part of the cotyledon. As will be discussed in detail in Part II, the maternal blood probably flows slower in the intervillous space in the subchorionic placental part than in the intervillous space in the remainder of the placenta. In this subchorionic part, therefore, optimal uptake of nutritional constituents from the maternal blood can take place. We therefore contend that the uptake of nutritional substances takes place chiefly in the subchorionic part of the cotyledon, where the paravascular capillary system has its widest spread (villous structures and reticular areas, alternating with long capillaries).

In the remainder of the placenta, particularly in the central and basal parts of the cotyledons, the structure is different. The paravascular capillary system is less extensive here, whereas the density of villi is considerably higher. The maximal possible quantity of fetal blood therefore circulates in this part of the cotyledon. Also, the flow of material blood of the intervillous space is greater in this part than in the subchorionic part. It is consequently probable that a maximal exchange of oxygen takes place in the basal and central parts of the cotyledon. Thanks to the more rapid change of maternal blood in this part, the villi here have an optimal oxygen supply. The fact that the circulation of maternal blood is

more rapid here is no objection because oxygen exchange is a rapidly completed process; moreover, the villous capillaries are separated from the maternal blood by the thinnest possible membrane.

Bøe[8] regards the paravascular capillary network as a buffer system against an increase in blood pressure in the case of an excessive flow of blood in a villous region. The excess of blood could then be drained off via the arteriovenous anastomoses without having to pass the villi. In our opinion a possible excessive supply of blood to a villous region cannot be a very great strain on the capillaries in those villi. The capillaries in the villi which, moreover, are capable of withstanding a considerable blood pressure[23] are undoubtedly able to cope with this supply because these capillaries are short and especially wide; they offer little resistance to a large wave of blood, which will consequently pass rapidly. In these considerations we do not seek to refute the possibility of a buffer function altogether but we do emphasize that this function must be a very limited one.

(References appear on page 165, following Part II).

Investigations on the vascular system of the placenta

Part II. The maternal vascular system

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WE EXAMINED 4 specimens, a uterus obtained during the fourth month of pregnancy and one obtained during the eighth month (both with the placenta in situ), a uterus obtained at approximately the end of term by extirpation immediately after cesarean section, and a uterus obtained on the seventh day of the puerperium after a 29 week pregnancy.

The first specimen was from a 36-year-old patient who underwent hysterectomy for carcinoma; she was approximately 3 months pregnant on the day of the operation. Immediately after extirpation of the uterus the fetus was removed after dilation of the cervix. The placenta remained in situ.

Via the uterine arteries, into which polyethylene catheters were inserted, the uterus was washed out with physiological saline under a pressure of 100 to 120 mm. Hg. The placenta was washed out with the aid of a syringe introduced via the umbilical artery. Both in the left and in the right uterine artery, 12 ml. of a blue plastic solution was injected under a pressure of 120 to 140 mm. Hg, while 1 ml. of yellow plastic solution was injected into the umbilical artery and 2.5 ml. of red plastic solution into the umbilical vein. After hardening in a 2 per cent formaldehyde solution, the uterus was bisected in such a manner as to place the incision through the center of the placenta. One half was corroded in a 30 per cent KOH solution, while the other half was used in preparing sections for microscopic examination.

The second specimen was obtained from a primipara, aged 27, who, after some 7 months of pregnancy, died suddenly during an attack of eclampsia. The cause of death was found to be intraventricular cerebral hemorrhage, and the fetus had died during the attack of eclampsia.

After extirpation of the uterus, the cervix was dilated and the fetus extracted, the placenta remaining in situ. The uterus and placenta were washed out in the manner described above. Into each of the two uterine arteries 30 ml. of red plastic solution was injected; 9 ml. of yellow plastic solution was injected into the umbilical artery, and 14 ml. of blue into the umbilical vein. After hardening in a 2 per cent formaldehyde solution the uterus was bisected through the placenta; one half was corroded in a 30 per cent KOH solution, while the other half was used to prepare sections for microscopic examination.

The third specimen was from a multipara and was obtained approximately at term. On account of a cervical carcinoma the uterus was extirpated after delivery of the child by cesarean section. The incision was made longitudinally in the median line so as to sever

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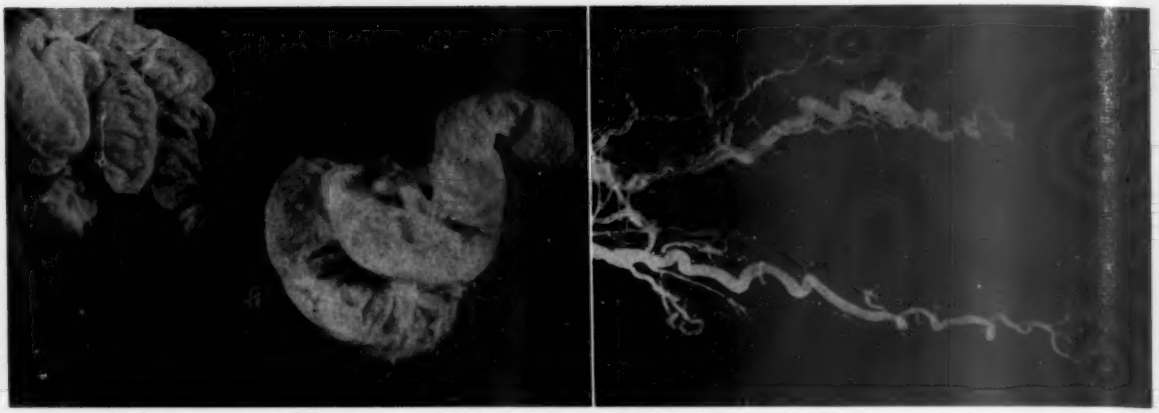

Fig. 1. A uteroplacental artery. Specimen from the fourth month of pregnancy. (Original magnification ×9.)

Fig. 2. Small uterine arterial vessels opening in the decidua outside the site of insertion of the placenta. Specimen from the fourth month of pregnancy. (Original magnification ×9.)

as few large vessels as possible. The uterus was washed out via the two uterine arteries and then injected with diluted red plastic solution under physiological pressure; blue plastic solution was injected via the two uterine veins. This was followed by hardening in 2 per cent formaldehyde solution and corrosion in 30 per cent KOH solution.

The fourth specimen was obtained from a 37-year-old primipara who died from pulmonary embolism on the seventh postpartum day. The child had been prematurely stillborn after detachment of the placenta. After extirpation, the uterus was washed out with physiological saline via both uterine arteries, after which 8 ml. of a thin plastic solution was injected under physiological pressure first through the right and then through the left artery. After hardening in 2 per cent formaldehyde the specimen was corroded in 30 per cent KOH solution.

Findings

In the uterine specimen obtained in the fourth month of pregnancy, that obtained in the eighth month, and that obtained at term, the arcuate arteries arising from the ascending branch of the uterine artery

Fig. 3. A uteroplacental artery passing into the intervillous space. Specimen from the eighth month of pregnancy. (Original magnification ×7.5.)

showed a larger diameter in the placental implantation region than did the corresponding vessels in the remainder of the uterus. This means that at the site of insertion of the placenta these vessels are hypertrophic (increased blood requirement at this site). Beker and Van Steenis[5] made similar observations on x-ray films of similar specimens previously injected with contrast medium.

In the uterus obtained on the seventh postpartum day this difference in vascular lumen was not visible; we therefore presume that this local hypertrophy rapidly recedes after parturition.

Local hypertrophy was found not only in the large uterine arterial vessels but likewise in the small vessels arising from the arcuate arteries and extending in the direction of the cavity of the uterus. At the site of the placenta these vessels—called uteroplacental vessels because they open into the intervillous space—were highly hypertrophic as compared with the corresponding arteries elsewhere in the uterus (Figs. 1 and 2). The uteroplacental arteries opened into the intervillous space beneath the entire basal plate of the placenta, at places showing no definite position relative to the cotyledons (Fig. 3). Fig. 4 shows a cast of the intervillous space injected via uteroplacental arteries.

Both in the corroded uterine specimen of the fourth month and in that of the eighth month of pregnancy, the plastic reappeared from the intervillous space in numerous places and merged with what could be described as a plexus (Fig. 5). Such a plexus gives a very definite impression of being venous. To verify this, sections were cut from the noncorroded half of the specimen at various places. It was then found that we were in fact confronted with a cast of the venous plexus which drains the blood from the intervillous space at numerous places beneath the placenta. Such venous drainage routes—uteroplacental veins—were very clearly seen to arise from the intervillous space beneath the entire basal plane of the placenta. Fig. 6 is a photomicrograph of a section obtained from the paramedian region of the placenta.

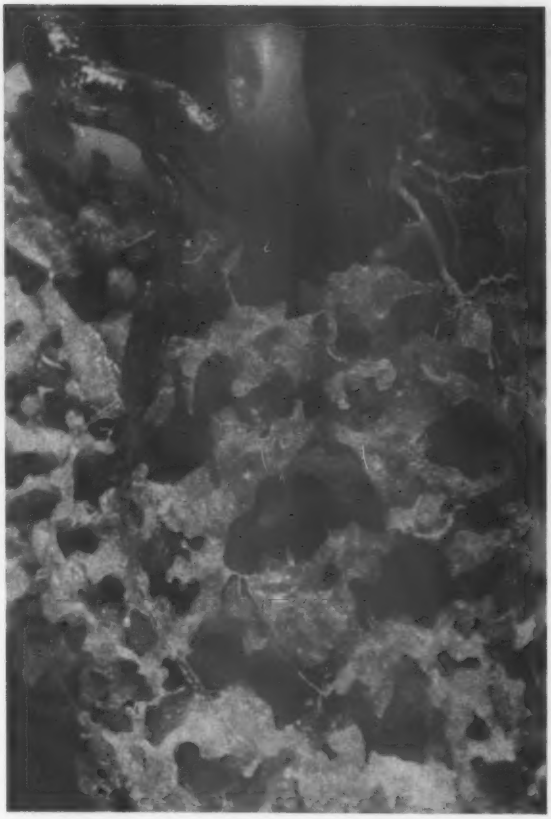

Fig. 4. Cast of intervillous space with a villous artery and vein. Specimen from the eighth month of pregnancy. (Original magnification ×7.5.)

It shows the intervillous space (right) merging with a large vein (left). Within the vein the plastic originating from the intervillous space is visible.

The draining orifices were found scattered at random over the basal plane of the cotyledon. As Fig. 5 shows, the veins constitute an extensive plexus, the structure of which becomes grosser as it approaches the surface of the uterus.

Like Ramsey,[28] we believe that the use of too thick an injection fluid prevented Spanner[37, 38] from finding any drainage routes beneath the placenta other than the marginal sinus with its efferent veins. The thick fluid in the intervillous space must have compressed the veins (which leave this intervillous space at an oblique angle, Fig. 6) rather than flowing into the vein. We used a thin plastic solution which was injected under physiological pressure and therefore more readily entered the uteroplacental veins.

Fig. 5. Transition from the intervillous space to uteroplacental veins beneath a centrally situated cotyledon. Specimen from the eighth month of pregnancy. (Original magnification ×3.)

In the peripheral part of the placenta in the uterus obtained in the eighth month of pregnancy we were able to demonstrate a paucity of villi; this region was filled chiefly with plastic (Fig. 7).

The plastic solution which entered the intervillious space via the uteroplacental arteries apparently found a suitable possibility of drainage in this peripheral zone; this is supported by the large, plastic-filled efferent routes connecting with the peripheral zone. This peripheral zone—which has also been clearly demonstrated by other investigators[15, 19, 25-29, 37, 38]—was most extensive in our specimen in that part of the placental periphery which borders the cervix uteri. It appears that this peripheral placental part is most markedly filled as a result of the force of gravity affecting the maternal blood; this part consequently shows most marked development.[34]

This peripheral zone (marginal lakes[27, 28]) is the peripheral portion of the intervillous space, bounded laterally by the chorionic membrane, below by the trophoblastic plate, and above gradually merging with the subchorial lake. Centrally it merges with the rest of the intervillous space.

Our findings, supplemented by observations from the literature, would seem to warrant the following view regarding the maternal circulation in the placenta. The maternal blood enters the intervillous space

Fig. 6. Transition from intervillous space to a uteroplacental vein, situated paracentrally beneath the placenta. Specimen from the eighth month of pregnancy. (Hematoxylin and eosin. Original magnification ×31.)

Fig. 7. Marginal zone. Uterus with placenta in situ from the eighth month of pregnancy.

via uteroplacental arteries opening at places beneath the entire basal plate of the placenta. The pressure under which this blood enters the intervillous space is 70 to 80 mm. Hg.[25] Consequently, the arterial blood in the intervillous space—where a pressure of about 10 mm. Hg prevails except during uterine contractions[2, 3]—is pressed in the direction of the chorionic plate (also during myometrial contractions[30]). A considerable portion of the maternal blood, however, does not reach the subchorionic part of the intervillous space but returns to the basal plate, from which it is drained via the uteroplacental veins. This drainage is accomplished since there is an additional fall in blood pressure between the intervillous space and the uteroplacental veins. The pressure differential is further enhanced by the intermittent myometrial contractions.[29] In this manner a definite circulatory region is formed again and again in the intervillous space of each cotyledon. These circulatory regions are separated by septa arising from the basal plate and extending as far as the subchorionic part of the intervillous space.

Since the septa do not extend as far as the chorionic plate, a communication between the intervillous circulatory regions of the separate cotyledons develops in the subchorionic part of the placenta. Part of the maternal blood contained in the intervillous circulatory region of a cotyledon does reach the subchorionic space and is added to the blood from the other cotyledonic intervillous circulatory regions. This blood moves in a lateral direction toward the peripheral zone, from which it is drained via uteroplacental veins.

In the placenta, therefore, we distinguish between the separate intervillous circulatory regions of the cotyledons, where the maternal blood circulates with a certain speed between the villi of the basal and those of the central part of the cotyledon, and the circulation in the subchorionic part of the intervillous space, where the maternal blood —flowing more slowly than that in the above mentioned circulatory regions—flows toward the periphery of the placenta.

Although Browne and Veall,[9] Kayser[21] and Borell, Fernstrøm, and Westman[6] claimed to have demonstrated that only the separate intervillous circulatory regions of the cotyledons exist in the placenta, it would seem to us to be more likely that there is also a subchorionic intervillous circulation. The peripheral zone with its large efferent uteroplacental veins—richly filled with plastic—points in this direction. The maternal blood in the subchorionic circulatory region flows chiefly to the lowest part of the

peripheral zone, i.e., the part located on the side of the cervix uteri.

The above data also show that the fetal vascular system has all the characteristics required if a large quantity of fetal blood is to be circulated rapidly. The capillaries of the separate villous capillary structures are short and wide, as a result of which the fetal blood meets no great resistance (wide capillaries) on its rapid passage through the placenta (short capillaries).

The inconsiderable difference in pressure between the umbilical arteries and the umbilical vein[31] can be largely explained on the basis of these facts. Since our investigation has shown the maximal density of villous capillary structures in the central and basal parts of the cotyledons (where the circulation of maternal blood is most intensive), we suggest that oxygen exchange is likely to take place preferably in this region. The rapidity of the circulation of highly oxygenated maternal blood in this region can be no objection because oxygen exchange is a rapidly completed process; the fetal blood in the villous capillaries, moreover, is separated from the maternal blood by the thinnest of membranes.

In the subchorionic part of the placenta, circulation of maternal blood in the intervillous space is considerably slower. The density of villi is less marked here than elsewhere in the placenta, but our investigation showed that the paravascular capillary network is more extensive in this zone. The paravascular capillary network—which in our opinion probably has a function in the uptake of nutritive substances—is thus localized in a region characterized by a slow flow of maternal blood low in oxygen, which fact promotes the uptake. The subchorionic part of the placenta, in our opinion, is therefore eminently suitable for the uptake of nutritive substances.

Summary

The fetal and maternal vascular system of the placenta was investigated, chiefly with the aid of the corrosion technique involving injection of specimens with plastoid or polymethylmethacrylate. In this manner we examined 65 human placentas and 4 uterine specimens (one obtained during the fourth month of pregnancy and one during the eighth month, both with the placenta in situ, one obtained at approximately full term, extirpated immediately after delivery by cesarean section, and one obtained on the seventh postpartum day, after 29 weeks of pregnancy).

Conclusions

1. Apart from the virtually constant anastomosis between the two umbilical arteries there are no arterial, venous, or arteriovenous anastomoses in the chorionic vessels.

2. A duplicate arterial supply to a peripheral cotyledon is a relatively rare anomaly; this was encountered in only 2 of the 65 specimens examined.

3. The villous vessels of the third order, which contribute to the fixation of the cotyledon in the basal plate of the uterus (choriodecidual vessels), occur throughout the entire basal plane of the cotyledon.

4. It is not the villous branches of the third order themselves which take a retrograde course in the direction of the chorionic plate, but only the terminations of these branches.

5. No arterial, venous, or arteriovenous anastomoses occur in the cotyledon.

6. There are no true anastomoses between the separate villous capillary structures of the villi; frequently, however, there is a connection between the separate villous capillary structures via capillaries of the paravascular capillary network.

7. The maximal density of capillaries is found in the central and basal part of the cotyledon. The subchorionic part—only 4 to 8 mm. thick—has a looser structural pattern.

8. The basic pattern of the villous capillary structures in the subchorionic part of the cotyledon is the same as that in the central and basal part of the cotyledon.

9. The inconsiderable difference in pressure between the umbilical vein and the umbilical artery can be explained largely on the basis of the inconsiderable resistance

in the capillaries of the villi, resulting from the shortness and considerable width of these capillaries.

10. The paravascular capillary system, the chief function of which is probably the uptake of nutritive substances, has its widest spread in the subchorionic part of the cotyledon.

11. The uteroplacental arteries open into the intervillous space beneath the entire placental surface, at random places relative to the position of the cotyledons.

12. The venous drainage of maternal blood from the intervillous space takes place as follows: (a) via uteroplacental veins arising from the peripheral zone (marginal lakes) and draining the maternal blood from the intervillous space of the subchorionic placental part; (b) via the uteroplacental veins, arising beneath the entire basal plane of the placenta at random places not connected with the position of the cotyledons and draining the blood from the intervillous space of the basal and central parts of the cotyledons.

13. In the intervillous space of the placenta it is possible to distinguish between the separate circulatory regions of maternal blood in the central and basal parts of the cotyledons and the circulatory region of maternal blood in the subchorionic part of the placenta, of which the peripheral zone is the constantly functioning draining region.

14. It is probable that the uptake of nutritive substances takes place chiefly in the subchorionic part of the placenta, while oxygen uptake is prevalent in the central and basal part of the placenta.

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Placental transfer of proteins in human gestation

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ONE OF the factors in the protection of the newborn is the antibodies received passively from the mother. The mechanism by which this transfer is accomplished varies in different mammalian species. The calf is born with agammaglobulinemia and obtains essential antibodies in the mother's milk during the first days of life. The mouse obtains some of its antibodies prior to birth, and the rest from its mother's milk. To complete the spectrum, the guinea pig and the human receive most of the maternal antibodies prior to birth (see Chapter IV in Brambell[1] for a review of this subject).

Morphologists noted that animals that transferred antibodies to their young prior to birth had "thinner" placentas, in the sense that there were fewer cell layers intervening between the maternal and fetal circulations. It appeared reasonable to assume that the transfer of antibodies resulted from the greater permeability of the thin placentas. Brambell and his co-workers[1] uprooted this theory when they demonstrated in the guinea pig and rabbit that the transfer of antibodies does not take place through the placenta at all, but through a modified yolk sac called the splanchnopleure or yolk sac placenta. Noting that in a wide variety of animals the transfer is accomplished by an entodermal organ, the yolk sac before birth or the gastrointestinal tract after birth, Brambell[2] called attention to the fact that there was no evidence that the route of transfer in the human was through the placenta which is mesodermal in origin. A possible alternative route was suggested—the transfer of maternal bodies into the amniotic fluid where they could be swallowed by the fetus and absorbed through the intestinal tract, which is entodermal. It was obviously of fundamental importance to an understanding of placental physiology that these possibilities be investigated.

There are only two routes available for the transfer of antibodies from mother to fetus. Antibodies may be transferred across the allantoic placenta into the umbilical circulation, or they may be transferred across the fetal membranes into the amniotic fluid. From here they could be swallowed and absorbed through the intestinal tract, as suggested by Brambell, or might conceivably enter the fetus through the pulmonary circu-

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lation. Evidence is presented in the following experiments that the transfer of antibodies, and possibly other proteins, to the human fetus takes places through the allantoic placenta, differing in this respect from the mechanism in most other animals in which entodermal organs accomplish this function. The only other exception described so far is the rhesus monkey.[3] Some of these data have been presented previously.[4]

Material and methods

Transfer of proteins during the first trimester. The experiments were performed on patients who were pregnant about 3 months and were scheduled for abortion for medical or psychiatric indications. Fifty microcuries of human serum albumin or gamma globulin labeled with radioactive iodine was injected 18 to 24 hours before operation. Lugol's solution was administered by mouth, 15 drops at the time of injection and twice more at 8 hour intervals to prevent incorporation into maternal or fetal thyroxin. Samples of maternal blood were withdrawn 15 minutes and 3 hours after the injection. At operation, samples of cord blood and maternal blood were collected and, when possible, amniotic fluid. Samples of amniotic fluid contaminated with blood were discarded. The "average" maternal radioactivity during the 24 hours of the experiment was determined by graphing the values obtained from the 15 minute, 3 hour, and 18 to 24 hour samples. Abortions were performed by vaginal or abdominal hysterotomy.

In two experiments, gamma globulin was injected into the amniotic fluid to investigate directly the transfer from the amniotic fluid.

Transfer of antibodies near term. Five milliliters of human serum containing a high titer of tetanus antitoxin was injected into the amniotic fluid 18 to 24 hours before elective cesarean section. At operation, samples of maternal and cord blood and of amniotic fluid were collected.

Preparation of materials. Human serum albumin* and gamma globulin† were iodinated by the method of Newerly.[5] The unreacted iodide was removed by passage through Dowex 1, 10 per cent x-linked, in the chloride form. The preparations were 99 per cent trichloracetic acid (TCA) precipitable and contained about 1 atom of iodine per molecule of protein. Paper electrophoretic analysis showed that the radioactivity was associated with the protein. The metabolic behavior of random lots was checked in rabbits and the results indicated that the proteins were essentially unaltered.

The high-titer tetanus antiserum (128 to 256 units per milliliter) was obtained from the Philadelphia Serum Exchange. It was obtained from a single professional donor who had received a booster injection of tetanus toxoid and who was considered free from serum hepatitis by history. The serum was checked before use for sterility and for pyrogenicity.‡

Analytical methods. The radioactivity was determined following precipitation of the plasma proteins with equal volumes of 10 per cent TCA. The proteins were washed with TCA, redissolved in normal NaOH and

Table I. Protein transfer in early pregnancy*

	I^{131} albumin		I^{131} gamma globulin	
	Fetus	*Amniotic fluid*	*Fetus*	*Amniotic fluid*
	14.0†	1.6	2.0	
	0.2	0.2	1.8	0.2
	0.05		84.0†	
	0.5	0.2	7.0	0.2
	0.4	0.3	1.7	
	1.1	0.8	1.7	1.0
	40.0†	0.9		
	0.8	0.4		
	1.2	0.5		
	5.4	0.4		
	4.4	0.8		
	0.9	0.7		
Average	1.36	0.6	2.8	0.5

*Radioactive proteins injected intravenously into mother 18 to 24 hours before samples were obtained. Transfer reported as: $\frac{\text{c.p.m./ml.}}{\text{average maternal c.p.m./ml.}} \times 100$.

†Omitted from average.

*Normal serum albumin (human), salt-poor, U.S.P., Cutter Laboratories.

†Globulin, poliomyelitis, immune, E. R. Squibb & Sons.

‡The pyrogenicity tests were performed by Lederle Laboratories.

the radioactivity determined in a well-type scintillation counter.

The antitoxin titer was determined by the mouse protection technique.[6]

Results

In Table I, the rates of transfer at about 3 months' gestation are presented as the ratio of the concentration of radioactivities of plasma proteins in the cord blood or the amniotic fluid relative to that in the maternal blood. The "average" maternal radioactivity during the 24 hours of the experiment was determined by graphing the values obtained from the 15 minute, 3 hour, and 18 to 24 hour samples. The values in the cord blood and amniotic fluid were determined from samples obtained at time of operation.

Several things are evident. Despite wide variation there is in general a small but significant transfer of proteins from mother to fetus. This is true of both albumin and gamma globulin, somewhat more of the latter being transferred on the average than the former. It is also evident that the concentration of radioactivity in the amniotic fluid is considerably lower than that in the cord blood.

In Table II are presented the results of two experiments in which gamma globulin was injected into the amniotic fluid. After 24 hours, there was significant radioactivity in the fetal blood but in much lower concentration than in the amniotic fluid.

To investigate the possibility of the transfer of antibodies to the fetus through the amniotic fluid near the end of pregnancy, high titer human tetanus antiserum was injected into the amniotic fluid 18 to 24 hours before elective cesarean section (Table III). After 24 hours, there was no detectable tetanus antitoxin in the cord blood. Titrations were carried to at least 10 per cent and in 3 instances to 2.5 per cent of the level in the amniotic fluid.

Comment

The injection of I^{131}-labeled albumin and gamma globulin into the maternal circulation at about 3 months' gestation resulted in low but significant transfers of these proteins into the fetus. The relatively poor transfer of proteins early in pregnancy correlates well with similar results in the rodent[7] and with the low titer of antibodies found in the cord blood of premature infants.[8] This contrasts with the more effective transfer of I^{131}-labeled gamma globulin late in pregnancy.[9] Despite some variability in the results, the transfer of gamma globulin appears to be more efficient than the transfer of albumin (Table I). Since the gamma globulin : albumin ratio in the fetus at this stage of pregnancy is much lower than in the mother, there is a more efficient exchange of fetal gamma globulin than of albumin.

The more effective transfer of gamma globulin suggests a selectivity of the transfer process even this early in gestation. A similar selectivity has been demonstrated late in gestation in the rodent[1, 10] and in the monkey.[3] The mechanism is obscure. It is not explained by molecular weight, that of gamma globulin averaging twice that of albumin. It is not known whether proteins other than gamma globulin are transferred at term in the human, but this seems likely.

Table II. Protein transfer in early pregnancy*

Fetal blood	*Maternal blood*
12.0	0
1.5	0

*The radioactive protein was injected into the amniotic fluid 24 hours before samples were obtained. Transfer is reported as: $\frac{\text{c.p.m./ml.}}{\text{c.p.m./ml. amniotic fluid}} \times 100$.

Table III. Transfer of tetanus antitoxin from amniotic fluid*

Amniotic fluid	*Cord blood*	*Maternal blood*
1.0	< 0.025	< 0.025
0.25	< 0.025	< 0.025
0.1	< 0.0025	< 0.025
0.1	< 0.0025	< 0.025

*Human tetanus antiserum was injected into the amniotic fluid 18 to 24 hours before elective cesarean section. Samples were collected at time of operation. Levels reported in units per milliliter.

Following the injection of radioactive plasma proteins into the maternal circulation, the concentration of radioactivity in the amniotic fluid was routinely lower than in the cord blood (Table I). For transfer to the fetus to occur through the amniotic fluid requires a concentrating mechanism in the fetus. In two experiments gamma globulin was injected directly into the amniotic fluid and, after 24 hours, the concentration of radioactivity in the cord blood was considerably lower than in the amniotic fluid (Table II). This excludes a concentrating mechanism, and thereby excludes the transamniotic fluid route as the major route early in pregnancy.

The question may be raised as to whether the protein-bound radioactivity found in the cord blood indicates transferred protein, or whether the radioactivity is split from the protein on the maternal side, transferred as inorganic iodide, and is rebound to fetal protein. Evidence has been presented previously[9] that in experiments of this design the protein-bound radioactivity represents transferred protein. The administration of Lugol's solution to the mother blocks the incorporation of liberated iodide into thyroxin, which could also appear in the blood as protein-bound radioactivity.

The investigation in term pregnancies was done with tetanus antitoxin because of our reluctance to use radioactive proteins in normal pregnancies when adequate information could be obtained otherwise. Human antiserum was used because animal experiments have demonstrated a difference in the efficiency of transfer of homologous and heterologous antibodies.[11] The risk of serum hepatitis was minimized by using serum from a single donor instead of pooled sera.

The results of these experiments (Table III) indicate that the absorption of antibodies from the amniotic fluid, if it occurs at all, is relatively inefficient and is inadequate to explain the transfer from mother to fetus.

The tenfold variation in titer of antitoxin in the amniotic fluid is probably the result of leakage at the time of injection. This does not affect the conclusions which are based on the titer at the termination of the experiment.

Following Brambell's interesting experiments in the rodent, it became evident that further investigation was necessary before a transplacental route for antibodies in the human could be accepted. Other investigations made unlikely a transfer route to the fetus through the amniotic fluid, but conclusive proof was lacking. Steigman and Lipton[12] found the poliocidal activity in the amniotic fluid much lower than in cord blood. Vahlquist[13] had demonstrated that antibodies are poorly absorbed through the gastrointestinal tract shortly after birth. Wasz-Höckert and others[14] reported a series of infants born with tracheoesophageal fistula in whom passively transferred antibodies were found in high titer. A study done in rhesus monkeys,[3] similar in design to this, demonstrated that radioactive plasma proteins are not transferred to the fetus through the amniotic fluid. The experiments presented here indicate that the human placenta, like the monkey's, is responsible for the transfer of proteins from mother to fetus, and that both differ in this respect from the rodent's despite certain histologic similarities.

Summary

1. Experiments in early pregnancy with radioactive plasma proteins and late in pregnancy with homologous tetanus antiserum have excluded the possibility that these proteins are transferred from mother to fetus primarily through the amniotic fluid and then by absorption through the fetal gastrointestinal tract, or through the fetal lungs.

2. The allantoic placenta is the only remaining route left in the human for transfer of proteins from mother to fetus. The human placenta, like the monkey's, is exceptional in being mesodermal and yet possessing the capacity for protein transfer. In most species this function is performed by an entodermal organ.

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Hypofibrinogenemia and presumptive amniotic fluid embolism associated with rupture of the uterus

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IN RECENT years there has been increasing recognition of the fact that certain pregnancy complications, notably abruptio placentae and prolonged retention of a dead fetus, may be accompanied by a coagulation defect of the blood as a result of fibrinogen depletion. Failure of the blood to clot has also been a frequent observation in reported cases of amniotic fluid embolism, and evidence to date indicates that the underlying process is one of defibrination. In addition, hypofibrinogenemia has been observed with cesarean section,[12] traumatic delivery, delayed postpartum hemorrhage, eclampsia, and hydatidiform mole, and has been reported in association with bacterial infections, surgical trauma, incompatible blood transfusions, and intravenous injection of a variety of substances, including certain plasma expanders.[8]

Although various theories have been advanced, the exact mechanism whereby defibrination of the blood takes place remains obscure. In essence there are two schools of thought, one holding that fibrinogen is used up as a consequence of intravascular coagulation following release of thromboplastic materials into the blood stream, the other favoring destruction of fibrinogen by a fibrinolytic enzyme.

The purpose of this paper is to report a case of spontaneous intrapartum rupture of the uterus complicated by severe shock and hypofibrinogenemia and to call attention to the probable occurrence of sublethal amniotic fluid embolism. The patient shortly before delivery experienced respiratory symptoms strongly suggesting amniotic fluid embolization. After a normal spontaneous delivery, exploration of the uterus disclosed rupture of the lower segment on the right side. Immediate hysterectomy was carried out but during the operation the patient remained in profound shock out of proportion to the amount of hemorrhage. Incoagulability of the blood was noted and the plasma fibrinogen level found to be significantly diminished. Massive transfusion, intravenous fibrinogen, and supportive therapy were administered and the patient survived.

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Case report

Mrs. R. O., a 30-year-old Negro woman, gravida viii, para vi, with estimated date of confinement of Dec. 24, 1959, had been followed in the prenatal clinic of the Norfolk General Hospital since August, 1959. The past obstetric history is of interest only in that the preceding

pregnancy ended in spontaneous abortion, for which a curettage was carried out in January, 1957. She was admitted to the labor and delivery suite at 5:05 P.M. on December 31, at which time she was in early labor with the cervix 3 cm. dilated and 75 per cent effaced, vertex at minus-1 station, and contractions of good quality at 4 minute intervals. The membranes had ruptured spontaneously approximately 36 hours before admission. Blood pressure was 100/60 and the fetal heart rate 144 per minute in the right lower quadrant.

At approximately 5:40 P.M. she complained of severe dyspnea and became quite apprehensive. At this time the blood pressure was noted to be 110/60 and the pulse 110. On auscultation the lungs were clear. The patient was then seized with a violent chill and her temperature was later found to be 103° F. The uterine contractions were now stronger than at the time of admission and progress to full cervical dilatation followed rapidly. In the interim a moderate trickle of bright blood from the vagina was observed. Meperidine (Demerol), 25 mg., and promazine (Sparine), 25 mg., were administered intravenously at 5:50 P.M. At 6:05 a 6 pound, 6 ounce infant was delivered spontaneously, no anesthesia having been given. The placenta followed at 6:10. There was no evidence of its having been prematurely separated. It was noted that there was a foul odor to the amniotic fluid.

About 30 minutes after delivery vaginal bleeding became excessive and an intravenous Pitocin drip was instituted. At this time the blood pressure had dropped to 84/40 and the pulse was 120. Inspection of the cervix revealed a laceration at the 7 o'clock position. At the apex of the laceration there was a small band of intact cervical tissue but above this was a rent in the musculature covered only by peritoneum. The patient was taken immediately to the operating room, where at laparotomy it was confirmed that the uterus had ruptured along the right posterolateral aspect of the lower segment, resulting in hemorrhage into the retroperitoneal space. A subtotal hysterectomy was carried out, during which time the patient remained in profound shock in spite of the fact that blood was being pumped into both arms. The blood pressure was unobtainable most of the time and the pulse ranged between 160 and 200. For a brief interval the systolic pressure was maintained at 100 by the addition of 4 c.c. of Levophed to one bottle of blood. Intravenous hydrocortone was also administered by drip.

After 4,000 c.c. of blood had been absorbed, the laboratory technician reported that blood drawn for cross matching had not clotted in 30 minutes. The observation was also made that subcutaneous swellings were present around the venipuncture sites and there was oozing from all cut surfaces. The plasma fibrinogen level* at this time was 140 mg. per cent and the prothrombin time 23 per cent of normal. Following administration of 2.42 Gm. prepared fibrinogen and an additional 1,000 c.c. blood, coagulation appeared to take place normally. At the completion of the operation the blood pressure had become stabilized at approximately 100/70 and the pulse was in the range of 100 to 110. Four hours after operation the fibrinogen level had risen to 234 mg. per cent.

Postoperative recovery was uneventful and the patient was discharged seven days later.

Comment

A survey of the literature reveals few reported cases of hypofibrinogenemia occurring with rupture of the uterus. As a matter of fact, the subject of clotting defects is not mentioned in several recent articles[3, 6, 16, 18, 26] devoted to uterine rupture.

In a review of fibrinogen deficiencies in pregnancy from the Los Angeles County Hospital, Longo, Caillouette, and Russell[13] mentioned two instances of ruptured uterus among their 48 cases, but gave no details concerning location of the rupture or associated findings.

Recently, a fatal case of rupture of the lower uterine segment with associated hypofibrinogenemia has been reported in the British literature.[23] Although the observed clotting aberration could not be explained, the possibility of amniotic fluid embolism was considered.

We have also noted a few isolated case histories exhibiting both rupture of the lower uterine segment and a coagulation defect (Cases 92 and 96 in Reference 14 and Case 6 in Reference 17). In these cases the patients developed profound shock

*Rapid method of Parfentjev, as modified by Fowell.[4]

comparable to that experienced by our patient. One of them (Case 6, Reference 17) survived following therapy that included fibrinogen administration.

In 1952 Ratnoff and Vosburgh[20] reported the first proved case of hypofibrinogenemia in association with amniotic fluid embolism. Their patient developed postpartum shock and hemorrhage, accompanied by hypofibrinogenemia, slight thrombocytopenia, and evidence of increased fibrinolytic activity of the blood. The occurrence of amniotic fluid embolism was subsequently demonstrated at autopsy. The authors confined themselves mainly to the hematologic aspects of the case and did not emphasize the fact that hysterectomy was carried out because of a laceration of the lower uterine segment.

It is our feeling that the striking similarity between our case and that of Ratnoff and Vosburgh is not mere coincidence. That the patient probably had amniotic fluid embolism (or infusion, as preferred by Reid, Weiner, and Roby[21]) seems logical for several reasons.

First, the sudden occurrence late in a rather precipitous labor of dyspnea with apprehension—but without pain, as in thrombotic embolism—is quite characteristic[1, 10, 25] if not almost pathognomonic.[22] Moreover, a severe chill followed the appearance of the respiratory symptoms. After delivery, the patient developed profound shock which was, in the opinion of several physicians in attendance, out of proportion to observed blood loss and which did not respond to massive blood replacement under pressure.

Second, in the present state of knowledge relative to coagulation defects, it is difficult to explain the hypofibrinogenemia on any basis other than amniotic fluid embolism. There was no evidence of premature separation of the placenta or of incompatible blood transfusion; nor was any plasma expander used. To postulate operative trauma as the cause would seem to have little to commend it, particularly since the fibrinogen depletion developed relatively early in the course of the operation.

There is perhaps one other conceivable explanation for the coagulation defect sustained by our patient; namely, the presence of infection. Hypofibrinogenemia has been reported in association with septic abortion[9, 13] and since the patient in this case undoubtedly had amniotitis we must acknowledge the possible role of infection. However, as suggested by Jackson and associates,[9] hypofibrinogenemia occurring with septic abortion could be due to the escape of thromboplastic substances from the uterus into the maternal circulation rather than to a specific bacterial toxin. To our knowledge it has not been demonstrated conclusively that a fibrinogen deficiency can be induced by infection per se.

Thus, in our opinion, infection was not important from an etiological standpoint. Since in many of the reported cases of amniotic fluid embolism the membranes had been ruptured for several hours or days, it is to be expected that infected membranes will sometimes be an associated finding. Under this circumstance bacteremia would be an inevitable consequence of amniotic embolization and would explain the sudden sharp temperature rise and chill that have occurred in some cases of proved amniotic fluid embolism. These symptoms were experienced by our patient soon after the initial dyspneic phase. Regrettably, a blood or uterine culture of the offending organism was not obtained.

As a final argument in support of the hypothesis that we were dealing with sublethal amniotic fluid embolism it appears to us quite plausible that the infusion of amniotic fluid was occasioned by rupture of the lower uterine segment late in labor. In their review of the first 26 reported cases of the syndrome, including 2 of their own, Kistner, Graf, and Johnstone[10] noted 5 instances of ruptured uterus. In these and in other cases associated with rupture of the uterus the laceration has usually occurred in the lower segment, with resultant retroperitoneal hemorrhage.

In an analysis of 15 cases of amniotic fluid embolism from the Minnesota Maternal Mortality Study, Barno and Freeman[1] re-

ported that rupture of the lower uterine segment was diagnosed twice.

Histologic evidence in support of the concept that uterine rupture is an etiological factor in amniotic fluid embolism has been provided by Landing,[11] who analyzed the uteri and lungs obtained post partum from a series of patients who had hysterectomies or who died after postpartum hemorrhage, cesarean section, or ruptured uterus, and from a control series of patients who died in the first postpartum week. His findings suggest that the escape of amniotic fluid into the maternal circulation is favored by conditions leading to abnormally opened uterine or placental vessels.

Pathologic study of the removed uterus in our case was carried out by one of us (W. M. P.) in an attempt to demonstrate epithelial squamous cells in the uterine vessels, as was done by Landing in his investigation. However, we were not able to find any unequivocal evidence of amniotic debris in the pathologic specimen. Nevertheless, since the lethality of amniotic fluid embolization is almost certainly correlated with the amount of particulate matter contained in the fluid, as indicated by the animal experiments of Steiner and Lushbaugh[25] with filtered and unfiltered amniotic fluid, our failure in this respect would not appear to invalidate our interpretation of the case as an instance of sublethal amniotic fluid embolism.

We conclude that the sequence of events in the above case report is best explained by postulating amniotic fluid embolization as a result of spontaneous rupture of the lower uterine segment in labor. Although admittedly the triad of ruptured uterus, hypofibrinogenemia, and shock not adequately explained by blood loss is rare in obstetric practice, we believe that the physician encountering a similar combination of events might be justified in presuming the occurrence of amniotic fluid embolism, provided other known causes of fibrinogen depletion (principally abruptio placentae) can be excluded. If, in addition, this clinical triad is preceded by the characteristic respiratory symptoms there can be little doubt of associated amniotic fluid embolization.

In the past there has been a hesitancy to make this diagnosis without pathologic confirmation. However, a number of cases of presumptive amniotic fluid embolism have now been reported.[2, 5, 7, 15, 19, 21, 24] We believe that a presumptive diagnosis can be made and, as postulated by Reid and associates,[21] some patients successfully treated by application of known principles. These would include combating of shock by the use of vasopressors, restoration of blood volume and administration of fibrinogen when indicated, adequate oxygenation, and prompt recognition and treatment of associated conditions, such as rupture of the uterus. In addition, adrenal cortical steroid therapy may be of value as a supportive measure.

Since tumultuous labor is recognized as a predisposing factor, and rupture of the lower uterine segment a probable mode of entry of amniotic fluid into the maternal circulation, we would urge that the possibility of the latter eventuality be kept in mind. Conversely, a diagnosis of lower segment rupture of the uterus should alert the obstetrician to the possible simultaneous occurrence of amniotic fluid infusion and the frequently associated disturbance in the coagulation mechanism.

Summary

1. A nonfatal case of spontaneous intrapartum rupture of the lower uterine segment complicated by hypofibrinogenemia and profound shock out of proportion to blood loss has been presented.

2. Arguments were offered in support of the hypothesis that this was an instance of sublethal amniotic fluid embolism.

3. Provided abruptio placentae and other known causes of fibrinogen depletion can be excluded, this hypothesis may also be applicable whenever the above clinical triad (lower segment rupture, hypofibrinogenemia, and shock out of proportion to blood loss) is encountered in the parturient.

4. Attention is focused on rupture of the lower uterine segment as a portal of entry of amniotic fluid into the maternal circulation.

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Coagulation defects in patients with abruptio placentae

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COAGULATION defects in patients with abruptio placentae have been recognized since 1901 when DeLee[1] reported the case of a patient with abruptio placentae who died because of uncontrolled bleeding. In 1936 Dieckmann[2] suggested that the coagulation abnormality in these patients was the result of hypofibrinogenemia. A milestone in the management of this obstetric problem was reached in 1949 when Moloney[7] reported the use of intravenous fibrinogen to control bleeding in patients with hypofibrinogenemia due to abruptio placentae. In recent years the literature on bleeding problems in patients with abruptio placentae has been voluminous and most authors have attributed the bleeding diathesis to hypofibrinogenemia.

The objective of this report is to describe our experience with coagulation problems encountered in managing 113 patients with abruptio placentae over a 3½ year period from July, 1955, through December, 1958, at the University of Miami School of Medicine—Jackson Memorial Hospital. A more complete description of these 113 patients, excluding details of coagulation abnormalities, has been published by Ferguson and Hatton.[4]

We found that an abnormality of coagulation was a more frequent and serious complication of abruptio placentae than has usually been described. There are three possible explanations for this: (1) The coagulation defects are concomitant with the frequency and the severity of toxemia at our hospital, that is, an incidence of 14 per cent[8]; (2) an assiduous search for coagulation deficiencies has yielded cases that otherwise would have escaped detection; and (3) strict criteria for the diagnosis of abruptio placentae eliminated cases of bleeding actually due to other causes, leaving us a group of cases of undoubted abruptio placentae, thus inevitably increasing the seriousness of the illness reported. Thirteen per cent of our patients had abnormal bleeding in extragenital areas that could not be explained by inadequate surgical hemostasis and/or from the postpartum uterus not explainable by hypotonia. Hypofibrinogenemia was frequent and, although it was not the only clotting factor deficiency, it is probably the most important single defect.

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Plan of patient study for coagulation defects

Our plan of study is to have all patients with the diagnosis of abruptio placentae, or even suspected of it, placed under a program of scrutiny for coagulation defects. Blood is drawn immediately for 3 laboratory studies: (1) a clot observation test, (2) a qualitative fibrinogen test, and (3) a quantitative fibrinogen test, and in addition, each patient is carefully observed for clinical evidence of a hemorrhagic diathesis. The results of these 4 observations show enough lack of correlation that we cannot place complete confidence in any one of them (Table I). Thirty-six patients had an ab-

normality in at least 1 of these tests but in only 9 of them were all 4 observations found to be abnormal. In 8 cases, 3 of the tests were abnormal, in 9 cases, 2 tests were abnormal, while in 10 only 1 test was abnormal. Until the hemorrhagic difficulties in abruptio placentae are better understood, we will have to continue to use this battery of tests.

Table I. Comparison of tests done to detect coagulation defects in 36 patients who had at least one abnormal test*

Case No.	*Clot observation*	*Qualitative fibrinogen*	*Quantitative fibrinogen*	*Hemorrhagic diathesis*	*Total positive results for each patient*
8	−	+	+	0	2
16	+	+	+	+	4
21	−	0	+	+	2
29	+	+	−	0	2
30	+	+	0	+	3
31	+	+	+	0	3
32	0	+	+	0	2
34	+	+	+	+	4
35	+	+	+	+	4
37	0	0	+	0	1
38	+	+	0	0	2
43	0	+	0	0	1
44	+	+	+	0	3
46	0	+	+	0	2
47	+	+	+	+	4
48	+	+	+	+	4
50	0	+	0	0	1
52	+	+	+	0	3
61	0	+	0	0	1
63	−	−	−	+	1
67	+	0	0	0	1
68	+	+	+	+	4
73	0	+	0	0	1
78	−	+	+	+	3
79	+	+	+	+	4
83	+	+	0	0	2
84	−	+	+	0	2
85	+	+	+	+	4
87	0	+	0	0	1
90	0	+	0	0	1
96	−	+	+	+	3
97	+	0	0	0	1
100	+	+	+	0	3
102	+	+	+	+	4
103	+	0	+	+	3
106	0	+	+	0	2
Total	20 (55%)	30 (83%)	23 (64%)	15 (41%)	

*Key: + = test indicates abnormality of coagulation; 0 = test indicates no abnormality of coagulation; − = test not done.

The clot observation test. This is simply the observation of the ability of the blood to clot in a test tube, and the character and stability of the clot when formed. This test is repeated at 30 minute to 1 hour intervals, depending upon the condition of the patient. In order to provide ready comparisons, the test tubes are attached with adhesive tape to the wall beside the patient's bed. If the blood fails to clot or shows evidence of lysis of the clot, we usually give fibrinogen immediately on the basis of this test alone.

The character of the clot was described in 50 of the 113 records of women with abruptio placentae. Clotting was thought to be abnormal in 20 of these patients in that 7 had poor clots, 10 had clots that lysed, and the blood from 3 failed to clot.

Qualitative fibrinogen test. At the time the blood is drawn for the first clot observation test, blood is also submitted to a qualitative fibrinogen examination using Fibrindex.* The results are available within 15 to 20 minutes and are reported as "normal" or "subnormal." We find a subnormal result usually indicates a fibrinogen level below 150 mg. per cent.

This test was done on 64 of the 113 patients with abruptio placentae. Thirty patients (27 per cent) had at least 1 specimen reported as subnormal. All except 1 of the 30 specimens with a subnormal qualitative test were also used for a quantitative test, and in only 3 of these 29 instances was the fibrinogen level above 150 mg. per cent. The character of the clot was described in 26 of these 30 cases with a subnormal qualitative test, and it was thought to be normal in only 5 of them. The blood from 7 patients formed clots that lysed, and in 3 cases the blood failed to clot. Twelve of these 30 patients with a subnormal qualitative test exhibited a hemorrhagic diathesis.

In order to evaluate further the reliability of the qualitative test, the results of the qualitative and quantitative tests on 194 specimens taken from the 64 patients with abruptio placentae were compared. The re-

*Ortho Pharmaceutical Corporation, Raritan, New Jersey.

sults failed to agree in 31 (16 per cent) of the specimens. We consider the quantitative fibrinogen determination in our laboratory accurate enough to be the standard. Therefore, we can assume that the error was in the interpretation or the accuracy of the qualitative test. In all except one pair of the disagreeing tests the subnormal qualitative test failed to be verified by the quantitative test.

Quantitative fibrinogen test. At least one quantitative fibrinogen examination was done on 66 patients, but this test was of limited value in the management of the patients because the results were not available for 8 to 24 hours. However, the quantitative fibrinogen test has been helpful in determining: (1) the accuracy of the clot observation test, (2) the value of the qualitative test, and (3) the cause of the hemorrhagic diathesis.

Twenty-three patients, 20 per cent of all of the women in our series, had fibrinogen levels below 150 mg. per cent. Eighteen of these 23 patients had fibrinogen levels below 100 mg. per cent; 2 had fibrinogen levels too low to be measured. The character or absence of the clot was described in the records of 18 of these 23 patients, and only 2 specimens were noted to have good clots. There was complete absence of clot formation in 3 cases, and the clots formed in 6 specimens lysed.

For further comparison of the clot observation with the quantitative test, the results in 154 paired specimens from 50 patients on whom both tests were done can be given. There were 25 (16 per cent) instances in which the clot observation test failed to indicate the depleted fibrinogen level. In 18 of these 25 paired specimens there was formation of a good clot, although the fibrinogen level was below 150 mg. per cent. It is interesting to note that there were 7 paired specimens with a fibrinogen level below 100 mg. per cent which formed good clots. Hodgkinson[6] has previously called attention to the group of patients who have abnormal quantitative tests but none of the anticipated bleeding difficulties.

Hemorrhagic diathesis. Thirteen per cent of all of the patients with abruptio placentae (15 women) had abnormal bleeding, as previously stated. Brief descriptions of the bleeding problems in these 15 patients follows:

1. Persistent bleeding from venipuncture sites, and from the uterus after cesarean section. Hysterectomy 1 patient.
2. Bleeding from gingiva and ecchymosis of the forearm, 1 patient.
3. Steady and abnormal amount of ooze from the postpartum uterus, 4 patients.
4. Bleeding from gingiva; petechiae on serosa of intestines; bleeding from uterus after cesarean section. Hysterectomy, 1 patient.
5. Abnormal bleeding postoperatively from an abdominal incision, 2 patients.
6. Abnormal bleeding from a cut-down wound, 1 patient.
7. Persistent bleeding from venipuncture sites, 1 patient.
8. Persistent ooze from postpartum uterus. Hysterectomy, 2 patients.
9. Five hundred milliliters of blood found on entering peritoneal cavity, origin not found. Abnormal bleeding from abdominal wound postoperatively, 1 patient.
10. Abnormal bleeding from cut-down wound and hematuria, 1 patient.

Quantitative fibrinogen levels were determined on 14 of the 15 patients with a hemorrhagic diathesis and only 1 patient had a plasma fibrinogen level above 150 mg. per cent; 11 had levels below 100 mg. per cent. A clot observation test was described on 11 of these 15 patients and it was abnormal in all of them. Blood from 2 of these patients failed to clot while 4 of them demonstrated fibrinolysins.

Fibrinogen therapy

On the staff service we have been inclined to administer fibrinogen if either the clot observation test or the qualitative fibrinogen test is abnormal. Fibrinogen has also been injected without waiting for the result of any of the tests when the patient has clinical signs of abnormal clotting. This liberality

with fibrinogen therapy has evolved from our experience of seeing patients become worse when one sign of abnormal clotting had failed to convince us fibrinogen was needed.

Twenty-four (21 per cent) of the 113 patients with abruptio placentae received fibrinogen. The dose ranged from 1 to 7 Gm.; the average was 3.8 Gm. The dose was dictated by the amount needed: (1) to control an abnormal bleeding tendency, (2) to produce a good clot in a test tube, and (3) to reverse a subnormal qualitative test to normal.

Dyer[3] reported that 7 per cent of 217 patients with abruptio placentae required fibrinogen. It should be noted that in the early years covered in his report, fibrinogen was not available for administration.

Among the 24 patients who received fibrinogen, the character of the clot was recorded in 20 of the patients' charts before the injection of fibrinogen. The clot was described as being normal in only 4 patients, while 2 demonstrated fibrinolysin, and no clot appeared in 3. Twenty-three of the 24 patients had a qualitative fibrinogen test which was subnormal in 21. The quantitative test was done on all 24 patients. The fibrinogen level was below 150 mg. per cent in 20 of the 24 patients. Of the 4 who did not have hypofibrinogenemia according to the quantitative test, the highest fibrinogen level was 196 mg. per cent. Seventeen of the patients who received fibrinogen had levels below 100 mg. per cent.

To our knowledge, only 1 of these 24 women had homologous serum jaundice. During her hospitalization for abruptio placentae, this patient received 5,500 ml. of blood as well as 5 Gm. of fibrinogen. Our follow-up on these patients is reasonably complete because of close contact with the patients' private physicians and the dominance of this hospital as the medical center for charity patients in the county.

Other coagulation studies

The occurrence of a bleeding diathesis in our patients with abruptio placentae has not correlated completely with their plasma fibrinogen levels. It was thought that a decrease in some of the other coagulation factors might play a part in the production of a hemorrhagic diathesis. In an effort to understand better the coagulation mechanism in patients with abruptio placentae, 25 patients were chosen at random and studied in Dr. John Miale's Coagulation Laboratory. The studies done included determinations of bleeding time, venous coagulation time, platelet count, observation of clot retraction, and, for evidence of lysis, one-stage prothrombin time, prothrombin consumption test, and the thromboplastin generation test. Together, these tests gave a good estimate of the known coagulation factors. A preliminary report[5] on these studies has been presented elsewhere and a detailed analysis of the data is forthcoming.

It was found that defects in the coagulation mechanism, other than decreased fibrinogen levels, were frequently present in varying degrees of severity. The results of these studies suggest that the more severe hemorrhagic problems probably occur when there is hypofibrinogenemia together with a deficiency in some of the other coagulation factors. These labile coagulation factors, together with platelets, are present in fresh whole blood. Therefore, we now administer fresh whole blood or fresh frozen plasma, if fresh blood is not available, in addition to fibrinogen in the patients with coagulation problems.

Summary

Our experience in managing the coagulation defects occurring in a series of 113 cases of abruptio placentae at the University of Miami School of Medicine—Jackson Memorial Hospital is presented. Hypofibrinogenemia is reported in 20 per cent and a hemorrhagic diathesis in 13 per cent of these patients. A special study of the mechanism of coagulation in 25 of these patients suggests that some of the other coagulation factors, in addition to fibrinogen, may be implicated. Fresh whole blood partially replaces some of the labile coagulation factors

and should be given with fibrinogen in patients with problems of coagulation.

I wish to express my gratitude for the assistance of John B. Miale, M.D., Professor of Pathology, University of Miami School of Medicine, and Director of Clinical Pathology, Jackson Memorial Hospital, Miami, Florida.

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Pregnancy complicated by asthma

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THE creation of an Obstetric-Pulmonary Clinic at The New York Lying-In Hospital in 1951 has afforded us the opportunity to care for a large number of asthmatic patients during pregnancy. This paper is a report of our experience with a view to answering the following questions: (1) How does pregnancy affect the asthmatic patient? (2) Conversely, what effect has asthma on pregnancy? (3) How should asthma be treated during pregnancy? (4) What special precautions are necessary in the management of the asthmatic patient during labor and delivery?

From Jan. 1, 1953, through Dec. 31, 1959, 293 pregnant patients with asthma were treated at The New York Lying-In Hospital. The incidence of asthma in all antepartal patients increased from 0.5 per cent in 1953 to 1.3 per cent in 1959. This increase was particularly marked in the past 3 years and was due to a greater awareness of and interest in this complication by members of the house staff. This resulted in the referral of more cases of asthma to the Obstetric-Pulmonary Clinic.

Clinical symptoms and signs

The most common clinical manifestations of asthma during pregnancy in our patients are listed in Table I.

Many patients had combinations of these symptoms, but some did not manifest the classical ones. Instead they complained of inspiratory wheezing and inability to draw in sufficient air.

How does pregnancy affect the asthmatic patient? The relationship between asthma and pregnancy is inconstant. Some symptoms of asthma, such as difficulty in breathing, orthopnea, and occasional cough, may occur in the pregnant patient without asthma. Hence their appearance during pregnancy, particularly in the last trimester, does not necessarily indicate the presence of asthma or its worsening. The majority of patients in our series, 271 patients, or 93 per cent, did not have severe asthmatic attacks during pregnancy and considered their asthma unchanged. Nine patients (3 per cent) stated that they required less medication for the control of symptoms and felt better. Thirteen patients (4 per cent) claimed their asthma was aggravated by pregnancy.

Attempts to determine a direct relationship between pregnancy and asthma are complicated by additional factors which occur coincidentally during the period of gestation. These are exposure to allergens, seasonal and climatic influences, upper respiratory infections, and emotional disturbances. Many of the 13 patients who had repeated attacks of asthma during pregnancy did so after arguments at home or other "nervous upsets."

What are the effects of asthma on pregnancy? The outcome of pregnancy in our asthmatic patients is shown in Table II.

There were 6 sets of twins; no therapeutic abortions were performed.

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Premature delivery. Twenty-six (8.9 per cent) of our patients were delivered prematurely. (Our definition of a premature infant is one weighing between 500 and 2,499 grams. It is based on weight only and not on the duration of pregnancy.) The factors responsible for prematurity are recorded in Table III.

Although prematurity appears to be slightly more common in asthmatic patients, 8.9 per cent compared with 6.2 per cent for all clinic patients during the period under study, if we correct for the 4 patients who had twins and the 2 patients who had induction of labor for severe preeclampsia, prematurity is reduced to 6.8 per cent in asthmatic patients.

A comparison of the etiological factors responsible for prematurity in our patients with those in a large series of cases of premature labor reported by Adam reveals a marked similarity.[1] In 43 per cent of his cases no known cause could be ascribed; in our series the figure was 46 per cent. In the category where the cause was known, which included antepartum bleeding, toxemia of pregnancy, and multiple pregnancy, Adam's cases totaled 52.5 per cent and ours 50 per cent.

There was no evidence that coughing, sneezing, respiratory distress, or other asthmatic symptoms were responsible for the onset of premature labor in our patients. The few patients who had severe asthmatic attacks during pregnancy did not have premature labors.

Abortion. Spontaneous abortions occurred in 11.0 per cent of patients with asthma, compared with 9.4 per cent of all clinic patients who had abortions during this period. In our patients abortion was not related to severe asthmatic attacks, nor were any deleterious effects noted from desensitization in 44 of our patients. An occasional case of uterine spasm or bleeding has been reported following antigen injection during pregnancy.[2-4] A survey in the literature of 202 pregnant patients who were desensitized during gestation showed that 11 suffered constitutional reactions but none had abortions.[5]

Management of asthma during pregnancy. The pregnant woman can be reassured that her asthma will have no bearing on her

Table I. Most frequent symptoms of asthma during pregnancy

Wheezing	115
Difficulty in breathing	95
Cough	86
Tightness in chest	29
Orthopnea	23

Table II. Outcome of pregnancy in asthmatic patients (1953 to 1959)

Delivery	*Asthmatic patients*		*Control*
	No.	*%*	*%†*
Full term	232	80.0	84.4
Premature	26	8.9	6.2
Abortion	32	11.0	9.4
Total	290*		

*Does not include 2 ectopic pregnancies and 1 undelivered patient.

†Per cent of all obstetrical deliveries at The New York Lying-In Hospital (1953-1959).

Table III. Factors responsible for prematurity

	Asthmatic patients		*Control series**
	No.	*%*	*%*
I. No known cause		46	43
Premature rupture of membranes	8		
Premature by weight only	3		
Intrauterine death	1		
II. Definite cause ascribed		50	52.5
Antepartum bleeding			
Placenta previa	3		
Premature separation of placenta	2		
Toxemia of pregnancy	4		
Multiple pregnancy	4		
III. Miscellaneous		4	4.5
Maternal febrile illness	1		
Total	26		

*One thousand, one hundred and eighty-six premature labors reviewed by G. S. Adams at University of Queensland Hospital, Brisbane.

pregnancy or on the outcome of her delivery. However, certain precautions should be observed. If desensitization has been instituted before pregnancy, it may be continued during gestation. Constitutional reactions may be avoided by not increasing the dose of antigen or spreading the injections over longer intervals. Advice should be given toward removing responsible agents or contributory factors that are known to produce attacks. Thus, pulmonary irritants such as dust, fumes, smoke, or cold air may trigger attacks. The asthmatic patient should not smoke, should avoid dusty trains or automobile trips, and should avoid fresh paint.

Exertion may also precipitate an attack. This is particularly evident in the last trimester when the respiratory excursions are limited by the enlarging uterus. Laughing or coughing may also cause an attack.

Infection plays an important role either as a primary or precipitating factor in asthmatic patients. At the first sign of a respiratory infection, a broad-spectrum antibiotic should be administered. The selection of the optimum antimicrobial agent should be determined on the basis of bacterial study of the patient's sputum. The argument for and against continuous antibiotic therapy has not been resolved. However, our personal preference is for a 7 to 10 day course of intensive antibiotics for each infection.

Some chronic asthma patients are able to control symptoms by the use of rectal aminophylline at bed time. Oral inhalation of a fine spray of ephedrine through a hand nebulizer when an attack seems imminent has been most useful. Antihistamines, particularly during periods of seasonal allergy, have given relief. At times a combination of aminophylline, ephedrine, and phenobarbital taken every 4 to 6 hours orally has controlled a mild or incipient attack.

The successful management of the patient who suffers an acute attack of bronchial asthma during pregnancy presents a dual problem to the obstetrician. His immediate concern is to relieve the symptoms promptly. Long-range management requires a careful study to determine the responsible antigens and to prevent allergic disturbances. While this long-term care falls within the province of the internist or allergist, when an asthmatic attack occurs during pregnancy or labor it may be necessary for the obstetrician to provide emergency treatment. No hard and fast rules are possible. Each patient must be treated as her individual situation dictates. However, the following measures are suggested as a starting point.

1. Reassurance and sympathy. Anxiety is an important factor in both pregnancy and asthma and becomes intense during an asthmatic attack. There is often a clear correlation between the relief of anxiety and the release of bronchial spasm. A calm, confident, sympathetic attitude on the part of the physician is most important.

Table IV. Treatment of severe, acute attack of bronchial asthma (Suggested order of use of antiasthmatic agents)*

Drug	*Dosage*	*Route of administration*
1. Epinephrine HCl	Inhalation of 1:100 dilution	Aerosol
or		
isoproterenol HCl	Inhalation of 1:200 dilution	Aerosol
2. Epinephrine HCl	0.2 to 0.3 c.c. of 1:1,000 dilution	Subcutaneous
3. Phenobarbitol	32 mg.	Oral
or		
pentobarbitol sodium	100 mg.	Oral
or		
chloral hydrate	0.5 to 2.0 Gm.	Oral
4. Aminophylline	500 mg.	Suppository
or		
aminophylline	500 mg. diluted in 20 c.c. water	Intravenous
5. Epinephrine gel	0.2 c.c.	Subcutaneous

*If no lasting relief is obtained, the patient should be hospitalized.

2. *Self-administered bronchodilator aerosols.* Three to 6 compressions of a hand bulb aerosol, such as 2.25 per cent racemic epinephrine or isoproterenol hydrochloride 1:200 may bring quick relief in a mild attack.

3. *Epinephrine subcutaneously.* A subcutaneous injection of 0.2 to 0.3 c.c. of a 1:1,000 dilution of epinephrine hydrochloride should be given if the aerosol is ineffectual. Large repeated doses of epinephrine should be avoided since chronic asthma patients suffering an acute attack may be epinephrine fast, at least temporarily.

4. *Sedation.* Phenobarbital, 30 mg., pentobarbital sodium, 100 mg., and chloral hydrate, 0.5 to 2.0 Gm., are sedatives usually well tolerated by asthmatic patients. Heavy sedation, particularly with morphine or other narcotics should be avoided since it depresses the respiratory center and may cause the patient to suffocate in her own secretions. It has no doubt contributed to death in some cases of asthma.[6] It is well to remember that in patients seriously ill, with anoxia and hypercapnia, sedation in any form may depress ventilation, leading to even greater respiratory insufficiency and carbon dioxide retention.

5. *Aminophylline.* For a mild attack a suppository of 500 mg. or 500 mg. administered rectally in 15 c.c. of tap water should be given. For a more severe attack, 500 mg. aminophylline in 20 c.c. of solution may be given intravenously.

6. *Epinephrine gel.* If lasting relief is not obtained in half an hour, 0.2 c.c. of epinephrine gel may be given subcutaneously. If no relief is observed in 10 minutes, the patient should be hospitalized.

Immediate treatment in the hospital. The reassurance a patient receives just from being admitted to a hospital and the knowledge that all facilities for treating her are available have resulted in spectacular improvement in the asthmatic attack before specific medication was given.

1. Treatment should start with an intravenous solution of 1,000 c.c. of 5 per cent dextrose in water containing 500 mg. of aminophylline. A total of 3 L. may be given within 24 hours. Adequate hydration makes the bronchial secretions less tenacious and corrects the electrolyte fluid imbalance.

2. The need for oxygen rarely occurs in the treatment of asthmatic patients. When it is necessary because of hypoxia, oxygen should be given by intermittent positive pressure, for example, with a Bennett respirator.

3. Relief of the bronchitic cough may be obtained by adding 1 to 2 Gm. of sodium iodide to each liter of infusion for several days. Steam inhalations of superinone (Alevaire) as well as ipecac and postural drainage may be of some value in ridding the patient of accumulated secretions.

4. At times bronchoscopic aspiration may result in spectacular improvement in the very ill patient whose bronchial tree contains inspissated, tenacious secretions. The establishment of an airway by this means and the administration of oxygen may be lifesaving in this type of patient.

5. For patients who are more than mildly ill, our internists at The New York Hospital advise frequent nebulization of bronchodilators and wetting agents with an intermittent positive pressure breathing device, such as a Bennett respirator, using compressed air, not oxygen.

6. Bronchial infection should be vigorously treated with a broad-spectrum antibiotic such as tetracycline.

7. When these conventional methods prove ineffective, adrenal steroid therapy may be considered. The exact mechanism by which these hormones alleviate asthma is not known, although they are thought to have an antiallergic and anti-inflammatory effect.[7, 8]

The following is the case history of a patient who had a severe asthmatic attack and required hospitalization while in the second trimester of pregnancy.

Patient M. P. This 33-year-old gravida ii, para i, had her first attack of asthma 7 months before her present pregnancy. When first seen in the eighth week of gestation she had severe wheezing, difficulty in breathing, a hacking

cough, and vomiting. These symptoms were apparently aggravated by the advice of friends that a therapeutic abortion was imperative to save her life. Reassurance, bronchodilators, and antihistamines gave her prompt relief, and, after 10 days, medication could be discontinued. She remained well for several months until an emotional upset triggered another attack. This episode was not relieved by the usual treatment and she was hospitalized.

She was given oxygen by mask immediately, and an infusion containing 20 units of ACTH and 500 mg. of aminophylline in 1,000 c.c. of 5 per cent dextrose in water. During the first 24 hours she received 3,000 c.c. of fluid intravenously, and ephedrine and amobarbital intramuscularly in repeated doses. Potassium iodide, small doses of meperidine hydrochloride, and aminophylline suppositories were also given.

Improvement was rapid and ACTH and intravenous medication was gradually decreased over a period of several days, during which time her symptoms completely disappeared. The remainder of the pregnancy was uneventful and she went into spontaneous labor at term. She was delivered by repeat cesarean section in early labor, the indication for the first section having been cephalopelvic disproportion. No further asthmatic attacks were reported up to 18 months post partum.

Comment. The decision as to when to use ACTH or corticoids in an asthmatic individual is difficult and depends on an evaluation of the entire allergy problem and the degree of morbidity in each case. If the asthma is seasonal, short-term use of oral corticosteroids is the logical choice. If the patient has a chronic, uncontrolled, intrinsic type of asthma and has not received steroids within the previous 6 months, ACTH may be preferable. In our patient the latter condition prevailed. No allergic basis for the asthma had been discovered, and the usual medicaments—epinephrine, aminophylline, sedatives—which had been successful in overcoming the first asthmatic attack, were of no help in this more serious episode. ACTH dosage was gradually decreased after alleviation of the symptoms. Steroids were not given at or immediately before cesarean section, since the dose used for the acute attack was small and more than 3 months had elapsed.

The outcome was not favorable in another patient admitted to the hospital in the second trimester of pregnancy in status asthmaticus.

Patient B. G. This 38-year-old gravida vii, para v, was brought to the Emergency Room with an acute attack of asthma. She had been successfully treated for a severe attack 10 months previously with intramuscular phenobarbital, subcutaneous epinephrine, and rectal aminophylline.

Although she had had asthma for 13 years, desensitization was not begun until January, 1959, 4 months before the present pregnancy. No reactions resulted from the desensitization injections, which were not increased during pregnancy and which were given at longer intervals. The patient stated that she had had hypertension in her last 3 pregnancies.

Treatment of the status asthmaticus included soluble phenobarbital, parenterally, on three occasions within a period of 2½ hours, epinephrine subcutaneously, and as an aerosol solution, aminophylline rectally and intravenously, oxygen by respirator, and intravenous dextrose in water with aminophylline. Her condition did not improve, and, in fact, she became more cyanotic; respirations were labored, more rapid, and shallower; and the cough was productive of small amounts of thick, mucoid material. She was kept in deep surgical anesthesia with ether and oxygen for 1½ hours in an attempt to relieve the bronchial constriction. Intermittent tracheal suction aspirated a thick, mucoid, frothy liquid. No improvement was apparent from this procedure.

Hydrocortisone, 100 mg., was given by intravenous drip and cortisone acetate, 75 mg. intramuscularly, and 500 mg. tetracycline intravenously 2½ hours later. Oxygen was administered by the Bennett respirator, and aerosols of isoproterenol and superinone were given intermittently with the oxygen. The blood chemistry report taken earlier showed the pH level to be 6.8. The patient's condition grew worse and she vomited and aspirated a large amount of brown material. She had several generalized seizures which were followed by apnea and cardiac arrest. The chest was opened and the heart massaged to no avail. At autopsy, thick mucous plugs were present in the bronchioles and bronchi.

Comment. This patient, with chronic asthma and known allergies, was admitted to the hospital in status asthmaticus. She did not respond to the usual medications or to administration of ether, or to intravenous corticosteroids. Opinions vary as to whether and when intravenous corticosteroids should be given. The consensus seems to be that ACTH and cortisone should not be used in the early treatment of a new case until the usual remedies have been tried for 24 hours. However, in patients with known asthma who develop status asthmaticus, some advise that intravenous steroids be given at once. Control of asthma is achieved sooner with intravenous steroids than with ACTH.[9]

A severe electrolyte imbalance developed in this patient and blood chemical determinations revealed a pH level of 6.8. This was an important factor in her death, as was the plugging of the respiratory tract with thick mucus.

The use of steroids as emergency treatment is not questioned. It is suggested that steroids be avoided in the pregnant asthmatic patient, particularly in the first trimester, except as a last resort. Although reports state that ACTH and cortisone administered during pregnancy did not increase the incidence of abortion and prematurity, alter labor, increase postpartum complications, or affect the fetus[10-12] extreme care should be exercised in their use, particularly in patients with heart disease, diabetes, pulmonary tuberculosis, etc. They should not be given to the patient with toxemia of pregnancy.[13]

The use of corticosteroids in the pregnant asthmatic patient will be discussed in a subsequent paper. It is of interest to note the outcome of pregnancy in 12 of our patients who received steroids during gestation for periods ranging from 4 days to 9 months. Of 7 patients who received corticosteroids in the first trimester of pregnancy, 4 had full-term, normal deliveries of living infants, 1 had a premature delivery of a 2,100 gram infant, 1 had a spontaneous abortion, and 1 had a missed abortion. The 5 patients who received cortisone in the second or third trimester of pregnancy had full-term, normal deliveries of live infants.

Management of labor and delivery. Asthmatic patients in labor should be questioned as to sensitivity to such common offenders as aspirin, codeine, barbiturates, morphine, penicillin, or sulfonamides, since these agents are frequently used for the parturient. Furthermore, sensitization may occur following the second administration of a drug after an interval of 1 to 4 weeks. This is particularly true of tetracaine.

In preparation for labor and delivery the patient who has been receiving cortisone may require a moderate increase in dosage.[14, 15] When labor begins, 200 mg. of cortisone is given intramuscularly. If labor lasts longer than 12 hours another 100 mg. of cortisone may be given intramuscularly. Following delivery, cortisone is gradually decreased to the maintenance dose or discontinued.

If cesarean section is planned, the patient is given 200 mg. cortisone 48 and 24 hours before operation and another 200 mg. on the morning of operation. Following operation the daily dose of cortisone is decreased gradually to the preoperative maintenance dose.

Type of delivery. Of the 264 full-term and premature deliveries, 168 (63 per cent) were spontaneous vaginal deliveries, and 96 (37 per cent) were operative. The latter included 23 per cent forceps deliveries, 8 per cent cesarean sections, and 6 per cent breech deliveries. The average incidence of operative deliveries in all clinic patients in the past few years was 39 per cent, of which 30 per cent were forceps deliveries, 4.5 per cent were cesarean sections, and 4.0 per cent were breech deliveries.

Although the incidence of cesarean section in the asthmatic patient was higher than that for all clinic patients, asthma per se was never an indication for cesarean section in this series.

Analgesia. Various analgesics including the barbiturates, promethazine hydrochloride (Phenergan), meperidine, morphine,

and scopolamine were used in this series. Our present preference is for small doses of a barbiturate followed by meperidine and promethazine. Promethazine is an excellent antihistaminic and in addition relaxes the patient and reduces the quantity of analgesics required. Although morphine was used in 9 patients in this series, we do not recommend its use in the asthmatic patient. Atropine should also be avoided since it is not an effective bronchodilator and its drying action on the mucous membranes of the bronchial apparatus leads to further inspissation of mucous plugs. Scopolamine has a more marked central sedative effect than atropine and it too is not recommended.

Anesthesia. The anesthesiologist should be informed of the fact that a patient is asthmatic, and should be told of all existing drug sensitivities. He must also be advised as to previous steroid therapy. Nitrous oxide, cyclopropane, and ethylene are safe for short periods since they cause little irritation to the respiratory mucosa. While ether is contraindicated for light anesthesia because it irritates the mucous membranes and increases bronchial excretions, it may be used for deep anesthesia. Spinal anesthesia is advised for cesarean section or extensive obstetrical procedures, although sensitivity to procaine may preclude its use. If it is used with general anesthesia, curare should be administered very slowly since it liberates a histamine substance from the body tissue.

The large majority of our patients were delivered under local and/or pudendal block anesthesia. Oxygen was given by mask during the second stage. When deep general anesthesia was necessary, cyclopropane was used.

Summary

1. The incidence of asthma in pregnancy is slightly over 1 per cent in all prenatal patients at The New York Lying-In Hospital.

2. Pregnancy has no marked effect on asthma. The large majority of patients showed no change in the severity of their symptoms during gestation. Three per cent of the asthmatic patients were improved and 4 per cent were worse.

3. A slightly higher incidence of abortion and premature delivery occurred in our asthmatic patients compared to the clinic population as a whole. We do not believe this is of any significance or directly attributable to the asthma.

4. Treatment of acute asthma during pregnancy has been outlined. This includes reassurance, epinephrine, sedation, aminophylline. If no improvement occurs within one hour, hospitalization is advised.

5. Hospital treatment for status asthmaticus has been suggested. This must be immediate and should be carried out in cooperation with the internist. Adequate hydration and attention to electrolytic balance is of great importance.

6. Adrenal steroids may be administered for severe asthma during pregnancy. They should not be used until all other medications have been tried.

7. Preparation of the patient who has been receiving cortisone for delivery or cesarean section has been outlined. A moderate increase in cortisone may be required at this time.

8. Vaginal delivery should be anticipated in the asthmatic patient. Morphine, atropine, and scopolamine should not be used for analgesia. Small doses of barbiturates, meperidine, and promethazine are recommended.

9. The anesthesiologist should be informed of the patient's drug sensitivities. Delivery under local or pudendal block with the patient receiving oxygen by mask is our method of choice. Either may be used for deep, but not for light, anesthesia. Cyclopropane may be used for general anesthesia.

We wish to thank Dr. R. Gordon Douglas, Professor of Obstetrics and Gynecology, for his many helpful suggestions. We are also indebted to Dr. Thomas Killip, III, and to Dr. Aaron Feder of the Department of Medicine of The New York Hospital for their advice concerning the medical aspects of this paper.

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Discussion

Dr. Thomas Killip, New York, New York. One of the recent encouraging trends has been the emphasis on the use of nebulizers in the mild asthmatic attack. The major problem in such patients is usually an acute bronchospastic episode and the patients often state that a few squirts of a handy nebulizer, carried in the purse or pocket, containing a 1:100 solution of epinephrine or similar amine compound will relieve this sudden mild episode.

Sedation, however, is a two-edged sword in the asthmatic patient. Many of them are apprehensive, as their asthmatic episodes have often been triggered by some presumably trivial emotional upset at home and mild sedation can be very effective. On the other hand, for the patient with severe asthma who is truly in status asthmaticus with severe ventilatory difficulty the use of sedation can be very dangerous. It can be shown in severely ill patients with asthma and ventilatory insufficiency that almost any form of sedation including phenobarbital or chloral hydrate can depress ventilation further, increase carbon dioxide retention, and cause further deterioration of the patient. One of the mistakes that was made, if it can be said to be a mistake, in the patient Dr. Schaefer presented, was in the Emergency Room. In a relatively short period of time 3 rather large doses of barbiturate were given to the very apprehensive, sick, excited, and yet dangerously ill patients. In retrospect, most of us who have reviewed this case report feel that excessive sedation helped to start the downward trend of more inadequate ventilation, more hypoxia, and more carbon dioxide retention.

The primary problem in the asthmatic patient is acute bronchospasm and inspissated mucus. In acutely ill patients we have had a rather extensive experience with the use of a positive pressure breathing device such as the Bennett with the nebulizer attached. This accomplishes two things: first, it ventilates the patient more because of the positive pressure drive of the cylinder of compressed gas; and second, the ventilatory device is so equipped that a large blast of nebulized drug can be forced deep into the bronchi. We have found a combination of bronchodilator (1:100 or 1:200 epinephrine) followed by a wetting agent to loosen secretions very successfully.

One is often faced with a serious dilemma when the patient does not appear to improve very much. In the patient Dr. Schaefer presented, surgical anesthesia with ether was attempted for over 90 minutes. Whether this helped or harmed the patient is a subject for great debate, but I think most of us would feel that anesthesia is truly a last resort to be turned to only when the cause seems totally lost.

The problem about steroids is raised frequently and we do not really know how effective they are. From skillful, dedicated hands, which means both good doctoring and good nursing, the simple measures such as reassurance and bronchodilators coupled with treatment of any infections are often very effective.

In the type of patient that we see in the hospital, desensitization as a rule has not been impressive. In the ambulatory patient with mild asthma the results of a kindly physician carefully administering desensitization procedures are often quite dramatic.

Dr. Sheppard Siegal, New York, New York. I would like to stress the value of the steroids in the treatment of bronchial asthma because I do not think they have been given their due

weight. Allergists generally resort to steroid therapy a little earlier than has been suggested in Dr. Schaefer's paper and our experience has been very favorable in the care of severe asthma. This does not apply to mild asthma which responds well to many other of the simpler measures so ably presented here tonight. However, if the patient shows a tendency to have recurrent asthma after being helped only briefly, or has a progressive course, or falls into the intractable group, we find that such patients do better on steroids, especially if they tend to go into status asthmaticus. In such patients steroids should be used early rather than late. If you defer them too long you might find yourself in a situation where you have almost no really effective remedy.

When a patient has severe status asthmaticus, steroids may be used as an emergency treatment intravenously and in adequate dosage. The intravenous and oral routes are likely to be more effective than the intramuscular route because the steroids are poorly absorbed from muscle.

Another point worthy of comment is the hesitancy in using steroids during pregnancy for fear of the effect upon the fetus. Most of the observations that have been made in recent years suggest that actually there is little or no ill effect on the fetus. I have seen patients who were taking steroids throughout the entire course of pregnancy and have been delivered of perfectly normal infants without any difficulty.

Dr. Aaron Feder, Great Neck, New York. The role antibiotics play in the control of an asthmatic seizure should be mentioned. Frequently the patient is asymptomatic until she develops an upper respiratory infection which is accompanied by tracheitis and bronchitis, following which the patient once again develops symptoms of asthma. These patients may do exceedingly well when the various measures recommended for the symptomatic relief of the bronchospasm and asthmatic symptoms are accompanied by appropriate antimicrobial therapy. Dr. Schaefer very wisely used the broad-spectrum antibiotics. This has true merit, first, because it is frequently not feasible or practical to do antimicrobial sensitivity studies of the sputum and because of the delay before cultural studies are completed; second, I think it is particularly appropriate to bear in mind the fact that the use of penicillin not only may be ineffective for the secondary bacterial invaders that supervene in a viral infection, but is of itself a dangerous modality.

One has but to recall the original paper that Dr. Kern wrote some years ago in the *American Journal of the Medical Sciences,* in which he reviewed instances of acute anaphylactic death following the administration of penicillin. He pointed out that every one of the 11 patients who died there had a previous history of asthma. Most internists today recognize that the administration of penicillin to a patient who gives a history of asthma carries with it a greater risk than to other patients, even though there may not be a specific history of sensitivity to penicillin itself.

The seriousness of the situation when the patient's condition changes from the state of simple asthma to the preterminal and sometimes fatal condition resulting from the plugging up of the respiratory tract with inspissated secretions likewise should be stressed. Asphyxia is frequently misdiagnosed by the inexperienced observer as status asthmaticus. Here the problem is one really of treatment of asphyxia per se, and unless one quickly provides the patient with an adequate airway for ventilation, the patient may be lost. These patients are frequently so far advanced in their state of asphyxia that they are already comatose and well anesthetized by their own carbon dioxide level. These patients can be served best by prompt recognition of the problem, and intratracheal intubation and aspiration of the bronchotracheal tree performed by the anesthetist. If this is unsuccessful, the prompt and sometimes repeated use of bronchoscopy may provide the airway, without which no additional measures can be of value. This is the first principle in the management of asphyxia from any cause, and applies no less importantly in the patient suffocating from the secretions in asthma.

Dr. Edward Solomons, Brooklyn, New York. About 2.5 per cent of the population in this country are afflicted with asthma and, as Dr. Schaefer pointed out, more than 1 per cent of pregnant patients.

Although asthma usually has no effect or very little effect on pregnancy and pregnancy has little effect on asthma, I think it is well recognized there are some cases of asthma actually precipitated by pregnancy. In our small experience we found this to be so and that in

more than 50 per cent of our patients the first attack actually occurred during pregnancy.

If there are 1 per cent or more of pregnant women suffering from asthma, one must assume that a certain number of these patients will have an associated toxemia. If an asthmatic pregnant patient also has toxemia, epinephrine should not be administered for it would be helpful for asthma but would be contraindicated for the toxemia. I would like also to raise the question of the possible dangers of corticoids in the treatment of asthma complicated by toxemia.

DR. SCHAEFER (Closing). The worsening of asthma during pregnancy is reported in the older literature but we could not find any large series in the recent literature to support this. As a matter of fact, there have been reports that asthma becomes worse only when the patient is pregnant with a female child and shows no change or gets better when she is pregnant with a male child. Dr. Silverman and I reviewed 66 charts of our 293 patients who had 2 or more pregnancies at The New York Lying-In Hospital. We could find nothing to substantiate this view.

Dr. Siegel also mentioned the use of corticosteroids early in an asthmatic attack. As a matter of fact, the original paper that we prepared contained a discussion of corticosteroids in pregnancy. Since this made our paper too long, we have decided to write a separate paper on this subject. I would only mention that I had a private patient in whom Dr. Feder did use ACTH immediately and she recovered spectacularly. She had been in status asthmaticus before being admitted to the hospital in the second trimester of pregnancy. In 12 patients who received steroids during pregnancy (cortisone was administered for periods from 4 days to 9 months) 7 were treated during the first trimester. Of these 7, 1 had a missed abortion, 1 had a spontaneous abortion, 1 had a breech delivery, and 4 had normal spontaneous deliveries. In 5 patients who received corticosteroids in the second and third trimester, all had normal spontaneous deliveries.

We agree completely with Dr. Solomons that cortisone should not be given to the patient with toxemia. I am sure that a patient with an asthmatic attack close to term will be able to breathe better after she has been delivered. However, if she is not ready for delivery we would not go about inducing labor or doing a cesarean section because of the asthmatic attack. We would rather treat the asthma just as we would any other medical condition in pregnancy.

Cerebral complications incurred during pregnancy and the puerperium

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COMPLICATIONS occurring during pregnancy and the puerperium have plagued mankind since the dawn of history. In recent years considerable attention had been drawn to the complications which implicate the central nervous system; these have disclosed the fact that such are not rare causes of death. Several reviews in recent years on cerebral complications occurring during pregnancy and the puerperium have emphasized the occurrence of such conditions as puerperal hemiplegia, subarachnoid and intracerebral hemorrhage, tumor and abscess, leptomeningeal and cerebral infectious processes, acute demyelinating diseases, and other neurological disorders. These reviewers have pointed out that signs and symptoms concerning the central nervous system, which have frequently appeared to be minor, are overlooked in the pregnant patient or are thought of as "just expected to occur." Consequently, they are not given the attention they deserve until other more obvious or more serious signs appear. As pointed out by Boshes and McBeath,[10] this neglect is particularly apt to be manifest in the case of minor cerebral infarctions that may occur during pregnancy and the puerperium. Later the infarcted area gives rise to seizure activity and only then is the true nature of the original episode recognized. The serious significance of meningeal symptoms consequent to subarachnoid hemorrhage has been emphasized by Cannell and Botterell[14] and many others. This and other catastrophic intracranial lesions occurring during pregnancy and the puerperium constitute a challenge to the neurosurgeon, that is, if the mortality and morbidity of these and other cerebral lesions is to be materially lowered. It seems worth while, therefore, to present a brief statistical analysis of fatal cases as well as a few examples of nonfatal cerebral complications personally encountered.

This paper details a study of all fatal cases which occurred in a limited area (Franklin County, Ohio) over a 10 year period. Through the cooperation of the very alert and active Franklin County Maternal Mortality Study Committee, the records of all deaths from 1948 through 1957 were reviewed. In this 10 year period there were 157,654 live births. There were 170 deaths which occurred during pregnancy, delivery, and the puerperium up to 6 months post partum. There were 36 maternal deaths attributable to complications primarily involving the central nervous system (23 per cent of all maternal deaths) (Table I).

To these series have been added nonfatal clinical cases of cerebral complications of pregnancies taken from the personal files of

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one of us (K. H. A.); these were not University Hospital cases. Fourteen nonfatal cases were found that occurred during pregnancy and the puerperium (6 months). It was soon apparent that not all cases with minor cerebral complications had been indexed and that those cases of cerebral vascular accidents occurring in the puerperium were not well cross-indexed. Therefore, only a few examples of subarachnoid hemorrhage, puerperal hemiplegia, and intracranial tumors will be presented to emphasize the importance of thinking of these conditions when any neurological sign or symptom appears in pregnancy and the puerperium.

The records of the Franklin County "Maternal Mortality Study Committee" have been used for this study. The cases observed were those in which death occurred during pregnancy or within a 6 month postpartum period. These cases have been divided into the following groups: subarachnoid hemorrhage, subdural hemorrhage, intracerebral hemorrhage, intracranial tumors, and a miscellaneous group of infectious processes, head injuries, etc. (Table II).

Table I. Franklin County (Ohio) maternal mortality study (1948-1957)

Total live births	157,654
Total deaths	170
Deaths due to central nervous system lesions	36

Table II. Intracranial causes of death

Intracranial tumors	9
Intracerebral hemorrhage	8
Subarachnoid hemorrhage	8
Viral or bacterial disease	8
Miscellany	3

Subarachnoid hemorrhage

Eight individuals died of subarachnoid hemorrhage during or shortly after pregnancy in this 10 year period from 1948 to 1957, inclusive (Table III). The ages ranged from 22 to 42 (3 each in the 20's and 30's and 2 in the 40's—41 and 42 years old, respectively). Six of these individuals had full-term deliveries; in the other two the hemorrhage occurred at the eighth and thirty-second weeks of gestation, respectively. Concerning the 6 with term deliveries, one apparently had a hemorrhage before going into labor, and was soon comatose; she was delivered in a respirator and died 2 days later. In 2 other cases, bleeding occurred about 3 hours post partum, and in one each it had taken place on the third, sixth, and thirtieth postpartum days. Twins were born to one patient whose symptoms appeared about 3 hours post partum. Six of these patients had had one or more previous pregnancies, the maximum being 5. In the last instance, there had been one abortion and 4 full-term pregnancies without previous signs of intracranial bleeding. None of these individuals lived over 6 days after the clinical onset of the subarachnoid hemorrhage. Of the 8 fatal cases, 4 patients died within 24 hours (one of which was dead on arrival to the hospital, having lived only a "few minutes"), and 2 each lived 3 days and 6 days, respectively.

It is of some interest that one patient (without previous pregnancies) had had an acute subarachnoid hemorrhage 18 months before, which was studied by bilateral carotid angiography and ventriculography with negative findings. Unfortunately, the vertebral-basilar arterial system had not been visualized and an interval angiographic study had not been performed. Interval angiographic studies should be done when vasospasm is less likely to be present; a search for a vascular anomaly is then more accurate.

In one patient the onset of hemorrhage 11 hours post partum was followed by angiography on the third postpartum day. A single aneurysm was visualized and clipped intracranially. The patient died on the sixth day after the hemorrhage. It may be that the interval from the onset of the hemorrhage to the performance of the angiography was too long, though it is usually not considered to be so. Hypothermia was not yet

Table III. Subarachnoid hemorrhage

Case	*Age*	*Previous pregnancies*	*Onset—stage of pregnancy*	*Survival period*	*Delivered*	*Previous subarachnoid hemorrhage*	*Diagnosis*	*Comments*
1	22	0	8 weeks	6 days	No	0	Subarachnoid hemorrhage	Negative angiography and ventriculography; no autopsy
2	31	3	Term and 3 days post partum	1 day	Yes	0	Subarachnoid hemorrhage	Lumbar puncture; no other tests; no autopsy
3	32	4	Term and a few hours	6 days	Yes (twins)	0	Subarachnoid hemorrhage, carotid aneurysm	Lumbar puncture; angiography; craniotomy; clipped aneurysm; autopsy
4	27	0	Term and 3 days	3 days ante partum and 1 day post partum	Yes, after subarachnoid hemorrhage	18 months previously	Subarachnoid hemorrhage	Lumbar puncture; negative angiography 18 months previously; autopsy
5	42	5	32 weeks	5 hours	Cesarean section	0	Subarachnoid hemorrhage	Lumbar puncture only
6	32	2	Term and 3 hours	3 days	Yes	0	Subarachnoid hemorrhage	Lumbar puncture only
7	41	1	Term and 1 day	1 day	Yes, 1 day after subarachnoid hemorrhage, in respirator	0	Subarachnoid hemorrhage	Lumbar puncture only
8	24	5 (1 ab. 4 term)	Term and 30 days	Few hours	Yes	0	Subarachnoid hemorrhage, carotid aneurysm	Dead on arrival at hospital; autopsy

being used in Franklin County Hospital at that time.

The signs and symptoms of subarachnoid hemorrhage in no way deviated from those found in other patients—headache and head pains, nausea, vomiting, neck stiffness, hemiplegia (in 3 cases), and bloody cerebrospinal fluid disclosed by lumbar puncture. It is unfortunate that more of these were not studied both by angiography and autopsy. It may be presumed in the absence of either diagnostic measure that all of these subarachnoid hemorrhages were consequently due to rupture of an intracranial aneurysm in the circle of Willis or its immediate branches. In view of the known bleeding tendency during pregnancy, this conclusion may or may not be correct. However, if this assumption is true, it appears that subarachnoid hemorrhage in the obstetrical period is peculiarly lethal.[81]

Intracerebral hemorrhage

The 8 fatal cases of cerebral hemorrhage are recorded in Table IV. As to age, there were 3 cases each in the third and fourth decades, and 2 cases in the fifth (each patient 40 years old). Eclampsia or preeclampsia were associated factors in three instances of intracerebral hemorrhage; there was necrosis of the hypophysis in one of these. Operative drainage of intracortical

blood clots was accomplished in the 2 noneclamptic patients and in one eclamptic patient. It seems doubtful that anything could have been done surgically for the 3 with intrapontine (brain stem) hemorrhages.

The symptoms in this group were headache, convulsion, hemiplegia, and coma, as well as the pre-existing and apparently causative arterial hypertension in both the eclamptic and noneclamptic patients. Each course was cataclysmic, being rapidly fatal except in 2 patients who survived 14 days each.

The precise cause of the intracerebral hemorrhage was not always ascertained although, in one instance, a small vascular malformation was discovered at the margin of a massive hemorrhage into a frontal lobe. In her review of this problem, Christensen[15] concluded that massive intracerebral hemorrhage occurs only consequent to alterations of vascular walls, a condition which may exist during pregnancy and the puerperium. She also points out that such hemorrhages (subarachnoid, intracerebral, intraventricular) frequently arise in intracerebral and intramedullary vascular malformations.

Subdural hematoma

There was only one instance of subdural bleeding. A nurse developed thrombophlebitis in the immediate puerperium in one lower extremity and was treated with anticoagulants (heparin and bishydroxycourmarin). In a grave condition, she showed signs of probable pulmonary embolism for which anticoagulants seemed justifiable. Nevertheless, she developed subdural bleeding which was not recognized until she became comatose. Her pupils soon became dilated and fixed and respiratory failure followed. Neurosurgical intervention was then obviously too late.

Intracranial neoplasms

In 9 instances, intracranial tumors were the cause of death (Table V).* There were 3 examples of astrocytoma (2 cystic), 2 of glioblastoma multiforme (astrocytoma Grade IV), 2 of meningioma (one malignant), one of an ependymoma and one of a malignant papilloma (both in the fourth ventricle). Two occurred in the second decade (ages 15 and 17) and 7 in the third decade (21 to 29 years).

The symptoms were few and practically unnoticed during pregnancy in 4 cases, but once they appeared they were rapidly fatal. The second day after the onset of headache and lethargy, one of the patients died of aspirating vomitus. This occurred 5½ months after a normal term pregnancy and delivery. Another patient went through pregnancy without a symptom, except for a few headaches, then 3½ weeks after delivery she suddenly experienced headache and vomiting. The neurological examination and a lumbar puncture with cerebrospinal fluid examination were reported as negative. Unfortunately, a convulsion occurred 5 days later and was followed by apnea and death within 24 hours. A parietal cystic astrocytoma with midbrain hemorrhage was found at autopsy. A malignant meningioma, which had remained silent until the sixth week post partum in another case, provoked a massive intracerebral hemorrhage which rapidly brought on headache and coma. In spite of prompt neurosurgical intervention, death followed. Without any known symptoms, one patient had a generalized seizure 1 hour post partum and died 2 hours later. The onset of symptoms of increased intracranial pressure or catastrophic manifestations occurred "immediately" post partum in one, one hour after delivery in a second, 3 weeks later in a third, 6 weeks after delivery in a fourth, and 5½ months post partum in a fifth. Symptoms occurred during pregnancy in 4 cases, causing premature spontaneous delivery in the first (at 7½ months) and surgical termination (cesarean section at 32 weeks) in the second. In the third, headaches, nausea, and vomiting began at 4 weeks' gestation, but the pregnancy went to term with spontaneous delivery. Operation was performed 3 weeks post partum when

*In addition to these, there are personal records on 2 more fatal cases, one an astroblastoma, and the other a low grade astrocytoma.

Table IV. Intracerebral hemorrhage

Case	Age	Onset		Longevity	Operation	Autopsy	Location of hemorrhage
		Term	Post partum				
9	29	Term	Undelivered	14 days	–	Yes	Intracerebral (eclampsia)
10	32	Term	Undelivered	18 hours	–	Yes	Intracerebral (pre-eclampsia)
11	20	6 months	Undelivered	12 hours	Yes	Yes	Intracerebral, right frontal lobe (necrosis of hypophysis)
12	40	Term	1 day	14 days	Yes	Yes	Intracerebral, right frontal lobe
13	34	Term	–	–	–	Yes	Intrapontine and subarachnoid
14	40	Term	2 hours	14 hours	–	Yes	Intrapontine
15	22	4 to 5 months	Undelivered	8 hours	–	Yes	Intrapontine
36	36	7 days post partum	7 days post partum	13 hours	Yes	Yes	Right parietotemporal

the patient was hemiplegic and comatose. Unfortunately, she failed to recover and died on the day of operation. Headaches were attributed to pre-eclampsia in the fourth (Case 34), and a dead fetus was delivered after labor was induced. A temporal lobe astrocytoma was resected 2 weeks later. Death followed several months later from infection.

Miscellaneous group—viral and bacterial infections

Tables VI and VII summarize the cases of a group of women who died of diverse causes. Included in these causes of death were infections (tuberculous meningitis, bacterial septicemia with meningitis, tetanus, cerebellar abscess, acute anterior poliomyelitis, toxoplasmosis, viral encephalitis), Guillain-Barré syndrome, anoxia (cardiac arrest), and trauma.

Nonfatal cerebral complications of pregnancy and the puerperium

Many neurological conditions are noted in the mother during pregnancy and following delivery; however, study is made of those cases of apparent cerebral thrombosis, intracranial hemorrhages (subarachnoid, subdural, and intracerebral bleeding), and intracranial tumors, since with our present knowledge these conditions might lend themselves to some type of definitive therapy. The pertinent data concerning these cases is found in Tables VIII to XI. There are not as many subarachnoid hemorrhages, intracerebral hemorrhages, and tumors in these cases as in the fatal ones. This may be due to such factors as inadequate cross-indexing of records, the sometimes obscure nature of lesions, and the tardiness in recognition of the symptoms. The absence of cerebral thrombosis in the mortality statistics as compared to findings in the 4 cases in the clinical group in which recovery occurred should also be emphasized (Table X). This suggests the need of adequate neurological investigation of all untoward symptoms during pregnancy and the puerperium referable to the brain, including ophthalmoscopic, x-ray, and electroencephalographic examinations, and, when indicated, examination of the cerebrospinal fluid, and in some cases angiography and air studies. A reduction in present mortality and improvement in results in nonfatal cases would be prompted by early diagnosis and appropriate therapy only when these investigations are promptly carried out.

General considerations

This study and that of Cannell and Botterell[14] would lead to the conclusion that subarachnoid hemorrhage is an extreme emergency and needs immediate neurosurgical attention. Earlier surgical interven-

Table V. Intracranial tumors

Case	*Age*	*Onset*	*Diagnosis*	*Course*
17	23	1 hour post partum	Parietal cystic glioma	One general seizure with rapid progression (2 hours) to coma and death
18	15	7½ month pregnancy	Intraventricular glioblastoma	Headache progressed post partum; craniotomy fifteenth postpartum day, death 15 days later
19	21	3 weeks post partum	Parietal cystic astrocytoma	Headache, nausea, and vomiting; lumbar puncture and neurological examination negative 5 days post partum; 19 days after operation general seizures and apnea; death 24 hours later
33	17	1 month pregnant	Temporal astrocytoma, Grade IV	Nausea and vomiting first month, right hemiparesis 1 month before delivery, hemiplegia by 3 weeks post partum, pneumoencephalogram and craniotomy; death 1 day after operation
34	28	First month of pregnancy	Temporal astrocytoma, Grade II	Pre-eclampsia, dead fetus with induced labor; headache 2 weeks, craniotomy, with multiple re-explorations for wound infection
16	29	5½ months post partum	Occipital meningioma	Blurred vision 2 days, then marked lethargy, aspiration pneumonia with immediate death
20	28	6 weeks post partum	Malignant meningioma, temporal lobe with massive hemorrhage	Sudden headache followed quickly by coma; craniotomy done, death in 24 hours
21	22	32 weeks pregnant	Malignant ependymoma, fourth ventricle	Headache, blurred vision and vertigo, diagnosis made; cesarean section and 12 days later craniotomy; death 36 hours after operation
35	23	Immediately post partum	Malignant fourth ventricle papilloma	1947 "burr holes for pseudo-tumor; postpartum headaches, blurred vision, diplopia; 50 days post partum craniotomy and ventriculosternal shunt; death 107 days post partum

Table VI. Viral and bacterial disease

Case	*Age*	*Onset*	*Diagnosis*	*Survival*
22	16	24 weeks pregnant	Tuberculous meningitis	1 month
22a	27	4½ months pregnant	Tuberculous meningitis	12 days
24	29	5 days post partum	Tetanus	7 days
26	38	31 weeks pregnant	Septicemia and meningitis	2 days
27	27	7 months pregnant	Cerebellar abscess from otitis media	15 days
28	37	17 days post partum	Poliomyelitis	30 days
29	25	Term	Toxoplasmosis	41 days
30	20	26 weeks pregnant	Viral encephalitis	1 week

tion with the routine use of hypotension and hypothermia and possibly newer methods to come may result in reduced mortality in this group.

It is believed that earlier diagnosis and surgical removal of intracerebral blood clots, of equal importance, will eventually produce much brighter results than recorded here.

Table VII. Miscellaneous neurological causes of death

Case	*Age*	*Onset*	*Diagnosis*	*Survival*
25	39	3 months pregnant	Cerebral contusion	16 days
31	19	2 months pregnant	Guillain-Barré syndrome	11 days
32	25	38 days post partum	Subdural hematoma	

Table VIII. Subarachnoid hemorrhage—nonfatal cases

Case	*Age*	*Previous pregnancies*	*Onset—stage of pregnancy*	*Delivered*	*Previous subarachnoid hemorrhage*	*Diagnosis*	*Comments*
1	38	0	8 hours post partum	Yes	None	Subarachnoid hemorrhage	Complete angiography negative; complete recovery
2	22	0	With labor	Yes	None	Subarachnoid hemorrhage and post-cerebral thrombosis	Complete recovery

Table IX. Intracerebral hemorrhage—nonfatal cases of cerebral complications of pregnancy

Case	*Age*	*Onset*	*Previous episodes*	*Complications*	*Diagnosis*	*Operations*	*Results*
1	33	10 days post partum	None	None	Intracranial hemorrhage, spontaneous	Angiography, craniotomy, ventriculo-jugular shunt	Hydrocephaly, blind
2	27	5 days post partum	None	None	Intracranial hemorrhage, spontaneous	None	Recovery
3	27	With labor	None	None	Arteriovenous malformation	Angiography, craniotomy	Minimal hemiparesis

Table X. Miscellaneous—nonfatal cases of cerebral complications of pregnancy

Case	*Age*	*Onset*	*Previous episodes*	*Complications*	*Diagnosis*	*Operations*	*Results*
1	27	3 months pregnant	None	None	Cerebral thrombosis	None	Hemiparesis
2	30	3 to 4 hours post partum	None	Pre-eclampsia	Cerebral vascular hemorrhage	None	Hemiparesis
3	27	3 months pregnant	None	None	Thrombosis internal carotid	Angiography	Mild hemiparesis
4	21	3 months pregnant	None	None	Thrombosis middle cerebral artery	Angiography and superior cervical sympathetic ganglionectomy	Mild hemiparesis
5	39	6 days post partum	None	None	Cerebral thrombosis	Angiography	Mild hemiparesis
6	29	5½ months pregnant	None	None	Trauma, skull fracture, subdural hematoma	Craniotomy	Personality changes, slight aphasia, hemiparesis

Cerebral thrombosis occurs all too frequently during pregnancy. This problem has been emphasized by Collier,[16] Martin,[54] Martin and Sheehan,[55] Symonds,[77, 78] Boshes and McBeath,[10] Alpers and Palmer,[2] and many others. It appears that this condition is not due to primary arterial thrombosis in all instances. Thrombosis of venous sinuses, or even a retrograde embolism from the pelvic veins via the paravertebral veins of Batson[5] (Martin[54]) may be responsible. This brings to light the problem of vascular wall and blood clotting changes that occur during pregnancy and the puerperium and may have a direct bearing on obstetric and puerperal thrombosis. Infection as a cause of cerebral venous thrombosis is not to be overlooked.

The instance of spontaneous subdural hemorrhage which resulted from the use of bishydroxycoumarin illustrates here the danger in the use of anticoagulants for thrombophlebitis. In this case, the situation was unrecognized until coma ensued. Consequently, the patient was referred for neurosurgical care too late to prevent a fatal issue. Earlier recognition of the neurological signs of clouding of the sensorium, mild hemiparesis, and early papillary changes might have prevented this fatality.

A somewhat different problem is presented in patients with intracranial tumor. Most investigators believe that the brain becomes edematous or in some way increased in volume during or immediately after pregnancy. This is apparently more true of meningiomas[3, 84] and acoustic neurofibromas[7] than of tumors of glial origin.[21, 63, 64, 68] Angiomas become engorged and are subject to thrombosis and hemorrhage. If hemorrhage occurs in or around such a tumor, the results may prove to be catastrophic, as in the case of a meningioma in the "fatal" series recorded above. Otherwise, the onset of symptoms may appear more gradually, requiring close and accurate observation. When these signs are recognized, appropriate neurosurgical attention must follow in this group of cases. Most neurosurgeons now appreciate the fact that pregnant patients with intracranial tumors soon develop more cerebral edema and other complications than the nonpregnant or nonpuerperal patients who have intracranial tumors. This observation suggests the need for further studies on cerebral edema, cerebrovascular states, and electrolytic balance in the obstetrical and puerperal periods.

Review of literature

General reviews. There have been many reviews concerning different aspects of neurological complications of pregnancy. Several reviews have dealt with the entire spectrum of complications. The reader is referred to these for a further general discussion of the intracranial complications of pregnancy and puerperium. Alpers and Palmer,[2] Boshes and McBeath,[10] Flicker,[32] King,[48] and Robb[68] have contributed significantly through their general reviews on the subject.

Table XI. Intracranial tumors—nonfatal cases

Case	*Age*	*Onset*	*Diagnosis*	*Course*	*Results*
1	27	Labor	Cerebellar medulloblastoma	Headache and diplopia, after delivery ventriculography, subtotal excision	Poor course, downhill
2	20	4 months pregnant	Cerebellar astrocytoma Grade II	Headache, lightheadedness, diplopia, vertigo, ataxia, ventriculography, craniotomy ventriculocisternal shunt	Poor course, downhill
3	24	6 years intermittent	Sphenoid ridge meningioma	Headache, blurred vision, no operation	No increase in symptoms, severity or frequency

Flicker[32] emphasized the role of arteriospasm as the productive agent of distal softening and encephalomalacia in the absence of chronic vascular disease. Robb's review[68] was particularly significant because of the detailed discussion of the significant physiological changes related to the incidence and etiology of subarachnoid hemorrhage, puerperal hemiplegia, and tumors occurring during pregnancy and the puerperium.

Eclampsia. The importance of the role of eclampsia in the neurological complications of pregnancy, particularly intracranial complications, has been frequently stressed. The role of eclampsia in cerebral hemorrhage has been much debated. Dieckmann[21] has stated that massive cerebral hemorrhage is not common in toxemia of pregnancy. He found that only 15 to 20 per cent of all autopsies performed on patients dying of fatal eclampsia showed extensive cerebral hemorrhage. He believed that the intracerebral hemorrhage was usually secondary to venous thrombosis. Sheehan and associates[73] found that approximately one third of the patients who died from eclampsia exhibited microscopic evidence of cerebral hemorrhage. Donnelly and Lock[23] studied 533 cases of fatal toxemia of pregnancy. In 393 of these cases the toxemia was found to be the direct cause of death. Cerebral dysfunction was found in 180 of the 533 cases. There were 89 instances of intracranial hemorrhage, 73 cases of sudden death preceded by respiratory arrest and cyanosis during convulsion, and 18 cases of coma with or without antecedent convulsions but without other explanation for death.

Oren,[61] in a paper published in 1951, stated, "Intracranial hemorrhage is more frequently associated with prepregnant hypertension than with the toxemic syndrome of pregnancy." Lane and Finn[50] reported an interesting and very well-documented case of postpartum eclampsia with subsequent cerebral hemorrhage. King[49] reported a case of a 19-year-old white multipara who died immediately after rupture of the lenticulostriate artery. Holmberg,[41] in 1949, emphasized the occurrence of encephalomalacia with toxemia of pregnancy and declared the pathogenesis to be a matter of small vessel spasm and subsequent changes in the vessel permeability. Parks and Pearson[62] studied the cerebral complications occurring in the toxemias of pregnancy. In their series of 8,457 deliveries, 1,009 patients showed clinical evidence of late toxemia of pregnancy. Forty-one of these showed typical eclamptic convulsions and 6 developed critical cerebral complications. The authors enumerated and discussed these complications as associated with encephalomalacia. It was their opinion that the encephalomalacia was secondary to the anteriospasm. They further stated that the cerebral edema, vascular thrombosis, and vascular rupture accompanying the toxemia of pregnancy result in the intracerebral and subarachnoid hemorrhages found so frequently in the cases of fatal toxemia. Robb[68] put forth the opinion that the generalized cerebral edema found in the toxemic patient was secondary to the physiological change of retention of fluid and sodium chloride.

Subarachnoid hemorrhage. There is a great deal of disagreement concerning the interrelationships of subarachnoid hemorrhage and pregnancy and the puerperium. In spite of many articles concerning this subject, the significance of the various phases of pregnancy, labor, and the puerperium as to the incidence of subarachnoid hemorrhage remains in question. Bleakney[9] calculated from available statistics that "approximately 40,000 members of the pregnant population might harbor potentially dangerous aneurysms." He stated that the rupture of an aneurysm in a pregnant patient was most likely when the blood pressure was increased, as in toxemia or hypertensive cardiovascular disease. He postulated that the likelihood of rupture is greatest when one of the following conditions is present: (1) during the time of the greatest blood volume, namely the seventh month of pregnancy; (2) on straining with the expulsive "bearing down" forces during the second stage of labor; and (3) when the uterus suddenly contracts following the end of the third stage of labor. Can-

nell and Botterell[14] presented an extensive discussion in reviewing this subject in 1956. It was their opinion that there was little or no connection between parity and subarachnoid hemorrhage or between the latter and the various stages of labor. They presented 16 cases of subarachnoid hemorrhage in pregnancy. These cases were drawn from a total of 61 consecutive cases of subarachnoid hemorrhage. There were 2 cases of subarachnoid hemorrhage associated with pre-eclampsia. One of these patients died after cesarean section delivery of a viable infant, while the other lived without sequelae following the vaginal delivery of a nonviable infant. Of the remaining 14 patients, one died 32 days post partum with a thrombosis of the superior sagittal sinus and another died 4 days after a septic abortion and showed sufficient evidence to warrant a clinical diagnosis of subacute bacterial endocarditis. Autopsy in this case showed a ruptured mycotic aneurysm of the basilar artery. In the 12 remaining patients, there were 6 cases of intracranial aneurysm, 3 arteriovenous malformations, and 3 subarachnoid hemorrhages of undetermined etiology. Thirteen subarachnoid hemorrhages occurred in these 12 patients, 7 of the hemorrhages occurred within the first 20 weeks of pregnancy, 4 during the last 20 weeks of pregnancy, and 2 in the puerperium. One of the last 2 died 2 hours post partum and the other 4 hours post partum. Further points of interest in this article were that 50 per cent of the patients with untreated subarachnoid hemorrhage died within 8 weeks. It was also noted that the second and third weeks following the original hemorrhage were the most common times of rebleeding. There were 16 deaths in the total series, 7 of these occurred during pregnancy and the puerperium; 6 of the deaths were in women with no recorded pregnancies. The authors advised prompt surgical treatment of accessible lesions. As stated above, it was their opinion that there was little connection between parity and subarachnoid hemorrhage and the various stages of labor. In a review of pregnancy complicated by subarachnoid hemorrhage, Schwartz[71] stated that parity was of no significance. He noted further that he had found no cases of subarachnoid hemorrhage occurring in the first two trimesters. He presented a total of 13 cases of subarachnoid hemorrhage following labor; there were 8 deaths. In only one case had the subarachnoid hemorrhage occurred during active labor. In 8 cases the onset was within the first 12 hours post partum, and it was within the next 24 hours in 3. Fifteen patients had the onset of hemorrhage before delivery; of the 15, 10 died. The prognosis of subarachnoid hemorrhage in the pregnant or postpartum patient was considered to be graver than in the ordinary nonpregnant patient. (In this series of 101 patients, there were only 18 deaths.) In the patients who became unconscious along with the onset of other symptoms, the mortality was 100 per cent. If unconsciousness was noted to supervene, the mortality was 86 per cent. In patients with subarachnoid hemorrhage and associated eclampsia, the mortality was 81 per cent. Magee[53] reviewed 150 cases of spontaneous subarachnoid hemorrhage and noted that 90 per cent of these patients had the onset of hemorrhage under no physical strain. Conley and Rand[17] studied 28 cases and found that hemorrhage in 4 patients occurred during labor, in 14 before delivery, and in 10 post partum. Of the hemorrhage occurring post partum in 10 cases, 6 took place within 24 hours of parturition; the maternal mortality was 42.9 per cent and the fetal mortality 26.3 per cent.

Christensen and Larsen[15] presented detailed studies of 5 very interesting cases of fatal subarachnoid hemorrhage in pregnant women with intracranial and intramedullary vascular malformations. Two patients were found to have ruptured aneurysms. One of these died 4 hours after the onset of hemorrhage and while in the ninth month of pregnancy, while the other was in the seventh month of pregnancy and died 1½ days after the onset of hemorrhage. A third patient had two episodes of subarachnoid hemorrhage. Angiographic studies were normal and the patient had no subsequent symp-

toms. A fourth patient died 4 days after the rupture of a hemangioma of the medulla. She was in the eighth month of pregnancy and was delivered 2 days after the onset of symptoms. The fifth patient died in the ninth month of pregnancy shortly after the onset of subarachnoid hemorrhage associated with a chromophobe adenoma of the pituitary gland. Richardson and Hyland[67] did a clinical and pathological study of subarachnoid hemorrhage and intracerebral hemorrhage caused by berry aneurysms. Three of their 126 patients were pregnant or in the immediate postpartum period at the time of hemorrhage. Strauss and Tarachow[76] presented 105 cases of subarachnoid hemorrhage, 2 of which occurred during pregnancy. One of these was in toxemia and subsequently died. In 1916, Fearnsides[27] reviewed 5,432 autopsies and found 15 aneurysms reported for a ratio of approximately 1:362.

Decker and Rowe[20] discussed the advantages of and the reasons for prompt ligation of the aneurysm even in the late months of pregnancy. Feldman and co-workers[28] examined the various aspects of the problem in a presentation of 5 case reports. Fleming and Mauzi[30] considered a case of spontaneous subarachnoid hemorrhage occurring in a woman, 28 weeks pregnant, who had normal angiographic studies and had no sequelae. Flexner and Schneider[31] discussed subarachnoid hemorrhage in the postpartum period following the injection of oxytocics. Garber and Maier[33] presented 3 cases of subarachnoid hemorrhage, one of which was in a patient who had toxemia of pregnancy. Gershenfeld and Savel[24] reported a case of subarachnoid hemorrhage on the third day post partum with minor symptoms and complete resolution. Hamby[37] reviewed 138 cases of subarachnoid hemorrhage, 75 in women; 4 of these were pregnant and 2 of the 4 died. Hyland[42] discussed the various aspects of prognosis in subarachnoid hemorrhage, particulary in the pregnant patient. Järvinen and Huhmar[45] presented a general discussion of nontoxemic subarachnoid hemorrhage during pregnancy, labor, and the postpartum period. Johnson[46] reported 4 cases of subarachnoid hemorrhage and discussed their various aspects, including the existence of pregnancy. Masten[56] described 12 cases of spontaneous subarachnoid hemorrhage; 2 of these occurred in pregnant women; 1 of the 2 had toxemia. Further interesting case reports have been related by Brehm,[12] Obler and Hurwitz,[59] Olivecrona and Riives,[60] Rhoads,[66] Russell,[69] Sands,[70] Speck,[74] Stone,[75] Trodella,[79] Walton,[82] and Weigle.[83] Trodella's[79] case was a carefully documented study of subarachnoid hemorrhage following the injection of intramuscular oxytocin and intravenous ergonovine maleate. Robb[68] has theorized that the generalized change that apparently takes place in fibrous tissue throughout the body during pregnancy may also occur in the wall of an aneurysm, with weakening of the structure and increased tendency toward rupture.

Intracerebral hemorrhage. Wagg[80] reviewed 10 years' cases of intracerebral hemorrhage and found 13 occurring in pregnancy or the puerperium. Of these 13 patients, 6 died. Of the 8 patients that were pregnant and suffered an intracerebral hemorrhage, 4 died. Of those in the postpartum period, 3 were more than 4 years post partum and one was 4 months post partum, having had no symptoms at the time of parturition. de Carle[19] reported 3 cases of cerebral vascular accidents unassociated with eclampsia in a review of 15,417 deliveries. He found 15 patients with eclamptic toxemia, 4 of whom had intracerebral hemorrhage. The studies of Dieckmann[21] and Donnelly and Lock[23] concerning eclampsia and intracerebral hemorrhage have already been noted. Goodfriend, Klein, and Smolev[35] reported 5 cases of pregnancy associated with hypertension and intracranial hemorrhage. The evident interrelationships of toxemia and hypertension were noted. It was stated that the presence of toxemia hastens the normal progressive changes of hypertension. The authors emphasized the importance of recognizing transient neurological symptoms as manifestations of organic intracranial disease. They pointed out that

these symptoms were often dismissed as clinical evidence of pregnancy, hypertension, and toxemia, without proper regard for the possible significance these symptoms might have in intracranial disease of serious import. Goodfriend and associates[35] also discussed the etiological significance of increasing blood volume during pregnancy and increased blood pressure during labor, particularly the fluctuations of blood pressure during labor. Greene and Barcham[36] warned against the use of vasoconstrictors in the patient receiving posterior pituitary extract or ergonovine. They quoted Melville who, in 1938, showed that posterior pituitary extract and ephedrine work synergistically in elevating blood pressure. Ephedrine further constricts vessels already constricted by posterior pituitary extract and prevents compensatory decrease in heart rate and cardiac output. Mack and associates[52] reported 3 cases and warned against the combined use of oxytocics and vasopressors, especially when spinal anesthesia was used. Fitzgerald[29] presented a study on a brand of methylergonovine tartrate (Methergine). In 200 cases, the administration of this effective oxytocic gave no significant alteration in systolic or diastolic blood pressure. Lane and Finn[50] presented an interesting report of postpartum eclampsia associated with cerebral hemorrhage. Lazard[51] published one of the earliest reports of cerebral hemorrhage in pregnancy in the American literature. His patient had headaches while in labor and lethargy during labor, followed by convulsions and coma that persisted until death 4 days later. Autopsy showed hemorrhage from a ruptured artery in the region of the corpus callosum. Moskowitz and Schneider[57] reported 3 cases of intracranial hemorrhage complicating labor and not associated with toxemia. Acosta-Sison[1] presented a very interesting case of extensive cerebral hemorrhage secondary to the rupture of a cerebral blood vessel due to the embolization of a portion of a chorionepithelioma.

Cerebral phlebitis. There have been several case reports of cerebral phlebitis. One of the most interesting is Symond's[77] case report of a thrombophlebitis of the dural sinuses and cerebral veins. Barraquer-Bordas[4] presented a comprehensive review about the puerperal cerebral thrombophlebitis syndrome. In 1956, Dubois[25] reviewed 18 observations previously published by Garcina and Destel and 29 other cases from previous articles. He concluded that the vessels involved were usually the superficial hemispheral veins and their associated sinuses in the parietal and frontal regions; seldom were the veins of the central brain and brain stem involved. He stated that the pathology is that of thrombosis followed by cerebral edema, subsequent interstitial extravasation of blood, and anoxia of the nervous tissue. He postulated that if the veins in the region of the Pacchionian bodies were involved, spinal fluid resorption would be obstructed with resulting intracranial hypertension. In the cases reviewed, 32 patients survived; but 9 of these showed significant neurological deficit. All 4 of the patients that had involvement of the great vein of Galen died. Dubois postulated that cerebral phlebitis is a primary vascular disease of the vein and not secondary to pelvic thrombophlebitis. Its onset is usually 2 to 3 weeks post partum and is manifested by convulsions and subsequent exacerbations and remissions of the symptoms of intracranial hypertension.

Thrombosis. Cerebral vascular thrombosis is one of the more common complications of pregnancy and the puerperium. Robb[68] felt that thrombosis was the primary cause of puerperal hemiplegia and was probably secondary to the increased thrombocytes, increased plasma fibrinogen, and increased viscosity of the blood which occurs in pregnancy and which he thought to be secondary to the presence of newly formed cells of premature type and large size. Batson,[5] in an excellent review, stated that one of the most overlooked but still quite frequent causes of cerebral occlusion was not venous thrombosis, but rather embolus. As opposed to Robb's[68] theory, Batson stated that these came from pre-existing thromboses in the pelvic veins, making their way into the cerebral circulation by way of the vertebral vein

system. In a case of cortical venous thrombosis following delivery, Bickel and Baran[8] found an extensive thrombosis of the cortical veins of both the superior sagittal and lateral sinuses which extended into the internal jugular veins. They postulated that venous slowing and alteration of the clotting mechanisms were the important etiological factors. Burt, Donnelly, and Whitener[13] reviewed the various aspects of thrombosis in pregnancy and the puerperium and found that a mortality of 30 to 50 per cent was usually reported in the literature. They discussed the typical picture of thrombosis in pregnancy and the puerperium. Further interesting case reports were by Dowie,[24] Hyland,[43] Kendall,[47] and Martin and Sheehan.[55]

Ellen[26] discussed encephalomalacia and its association to cerebral thrombosis. He stated that the syndrome of spasm and resultant encephalomalacia, with or without hemorrhage, was the most frequent correct explanation for the cerebral vascular accident in the pregnant woman without pre-existing hypertensive cardiovascular disease, lues, or congenital aneurysms.

Brain tumors. Bernard[6] in 1898, was the first to report the occurrence of a brain tumor during pregnancy. He noted that the diagnosis of brain tumor was not entertained until the symptoms of increased intracranial pressure persisted following delivery. This first case report was that of a 26-year-old white woman with a cholesteotoma of the right cerebral hemisphere. He reported a second case in 1899 of glioma of the right optic tract in a patient, 5 months pregnant, who subsequently developed hemiplegia and died.

Rand and Andler[64] published a comprehensive review concerning the relationship of brain tumor and pregnancy. They reported 12 cases which were extremely well documented. One patient was 5 months pregnant and developed an astrocytoma of the pons with subsequent death. The patient's pregnancy had been preceded by symptoms of bilateral tinnitus which was ignored before and during the pregnancy, the significance being realized only after delivery. Another case reported by these authors was of a 41-year-old patient, 7 months pregnant, who had astrocytoma of the frontal lobe. Death was preceded by unsteadiness of gait for approximately 6 weeks. A 17-year-old girl, 7 months pregnant, suffered hemorrhage into a cystic astrocytoma of the left cerebral hemisphere with subsequent death. In this case, the patient had noted progressive occipital headaches which had started 6 weeks after the last menstrual period. Another case was that of a 20-year-old woman, 1 day post partum, who had had a 1 year history of right-sided tinnitus, increasing deafness, blurred vision and unsteady gait with a tumor suspected only when the symptoms persisted post partum. The diagnosis was made shortly after delivery, and a right acoustic neurofibroma was removed. A 27-year-old white woman had gone through 2 successful pregnancies with a known meningioma of the sphenoid ridge; the tumor was successfully removed by the authors. Another case was that of a 25-year-old white woman who had undergone a subtotal excision of a "cerebellar cyst" approximately 5 years before parturition. Seven years after delivery, symptoms recurred. Further follow-up was not noted. A report of a 19-year-old white woman was included. She had a normal pregnancy and delivery 14 months after the evacuation of a gliomatous cyst of the left occipital lobe, but noted recurrence of symptoms approximately 4 months after delivery. A 32-year-old woman had a pituitary tumor which was manifested by visual symptoms during the seventh month of pregnancy. She was delivered at term and treated successfully with radiation. There were 4 other case reports. One was of an undiagnosed tumor with death occurring 4 hours post partum; another case was of pseudotumor cerebri in a patient who had had 2 normal pregnancies and deliveries; and a case of an unoperated cerebral vascular malformation which had been found when the patient was 7 years of age. Another patient had a long history of Jacksonian seizures and, following normal pregnancy and de-

livery, had a subarachnoid cyst of the left premotor area removed. The authors concluded that cesarean section should be done whenever a tumor is diagnosed because of the increased intracranial pressure that occurs with normal labor. They also advised that prompt intervention is indicated if a glioma is present. Cushing and Bailey,[18] in 1928, published a case of a midcerebellar cystic hemangioma in a pregnant patient who had had headaches and vomiting of severe degree prior to delivery. These symptoms were dismissed as being manifestations of pregnancy and not until they continued post partum and became accompanied by rapidly failing vision was the tumor diagnosed. Divry and Bobon,[22] in 1949, reviewed 74 cases, previously published, in which brain tumors occurred in the pregnant patient. Eighty per cent of the cases showed marked increase in symptoms during the second trimester with subsequent decrease post partum. In the other 20 per cent, the symptoms were increased shortly after delivery. In an article on meningeal tumors in 1931, Bailey and Bucy[3] cited a case report of a meningioma of the left frontal convexity which was not recognized until the eighth month of pregnancy when the patient began having convulsions. At that time, diagnostic work-up revealed the presence of the tumor. Shanks[72] reported the case of a 33-year-old white woman whose symptoms appeared during the second month of pregnancy. This patient was found to have a right cerebellar astrocytoma which was successfully removed prior to delivery. Reeves[65] reviewed a great deal of foreign literature in a very comprehensive article and suggested that each case should be given individual treatment and that generalizations could not be made. Jacobi[44] reported a case of cystic tumor of the left temporal lobe occurring in a patient who was 3 months pregnant. Other interesting articles and case reviews were noted by Alpers and Palmer,[2] Botreau-Roussel and Gourioud,[11] Hanssen,[38] Hendricks,[39] Hilker and Miale[40] and Whitcher.[85]

Nolen[58] presented a case of pseudotumor cerebri occurring in a 40-year-old white woman with 2 viable offsprings. Symptoms had developed during the twelfth pregnancy and consisted of right hemiplegia, nerve palsy, and left-sided headaches. These symptoms occurred toward the end of pregnancy, but completely resolved a few weeks after delivery. During the thirteenth pregnancy, no symptoms occurred and the pregnancy ended in abortion. A fourteenth pregnancy was productive of the same symptoms which occurred during the twelfth pregnancy but with progression into coma. A cesarean section was carried out and the patient recovered completely. Nolen[58] quotes Oppenheim concerning another case of apparent pseudotumor cerebri which was clinically diagnosed as hydrocephalus. The patient went through 2 pregnancies, but death occurred after the third. A postmortem examination showed chronic internal hydrocephalus, hydrops of the medulla oblongata, chronic pachymeningitis, and arachnoiditis with many adhesions.

Summary

In a statistical study of maternal mortality in Franklin County, Ohio, with a total of 170 deaths in a 10 year period (1948-1957), there were 36 fatal cases with cerebral complications of various types. Intracranial hemorrhage accounted for 17 deaths; subarachnoid hemorrhage, 8 deaths; subdural hemorrhage, 1 death; and intracerebral hemorrhage, 8 deaths. There were 9 cases of intracranial tumor with death. In a miscellaneous group of "cerebral deaths," infectious processes including tuberculous meningitis, purulent meningitis, brain abscess, acute (cerebromedullary) poliomyelitis, "viral" encephalitis, toxoplasmosis, and tetanus caused 8 of 10 deaths.

In a smaller clinical (nonfatal) group of 14 cases with cerebral complications occurring during pregnancy and the puerperium, 2 patients with subarachnoid hemorrhages made spontaneous recoveries. A diagnosis of intracerebral hemorrhage was made in 3 instances, in 2 of which operation was performed and evacuation of blood clots was

accomplished. In one patient spontaneous recovery occurred from a minimal hemorrhage. Five other individuals suffered from cerebral thrombosis, 3 in the third month of pregnancy and 2 in the immediate puerperium. All of these recovered with some residual deficits. Three instances of intracranial tumor were successfully treated surgically but with disappointing results ultimately (one case each of cerebellar medulloblastoma, cerebral astrocytoma, and supratentorial meningioma).

The literature pertaining to cerebral complications of pregnancy has been reviewed and summarized.

Only when the obstetrician, neurologist, and neurosurgeon are fully aware of the signs, symptoms, and many times the rapid course of these cerebral complications of pregnancy can there be any material lowering of the morbidity and mortality.

It is believed that emphasis should be placed on the early investigation of all neurological complaints during pregnancy and the puerperium with immediate institution of an aggressive diagnostic and therapeutic regimen.

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Spontaneous nontraumatic retinal detachment in pregnancy

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THE occurrence of spontaneous retinal detachment in pregnancy is a rare and unusual complication. In the past it has prompted the immediate termination of the pregnancy, and in some instances led to elective sterilization of the patient. This was deemed advisable in an attempt to prevent subsequent ocular damage with future pregnancies. The infrequent occurrence of this condition does not ordinarily permit conclusive reflective investigation. We have therefore reviewed the cases seen during the last 21 years at Charity Hospital, with an aim to present incidence, etiology, treatment, management of pregnancy, and possible prevention.

A review of the literature revealed few articles in the English language with reference to this subject. Hallum[3] in 1936 reported an incidence of 2 per cent, a figure that appears to most observers to be exceedingly high. Wagener,[8] at the Mayo Clinic, in 1933 was able to report only 2 patients with spontaneous, nontraumatic retinal detachment. Schiotz[5] in 1919 found 7 cases in 158 women with severe pre-eclampsia or eclampsia. Singh and Bruce[6] and Wahrsinger[7] each reported one case associated with severe toxemia of pregnancy. Kronenberg[4] reported 2 cases in 20,538 pregnancies. These cases were also in patients with severe pre-eclampsia.

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Material and methods

During the years 1937 to 1959 there were 10 cases of spontaneous nontraumatic retinal detachment associated with pregnancy, in 185,244 deliveries, or an incidence of 1:18,524 (Table I). All occurred in Negro women. This may be due to the fact that about 85 per cent of all admissions to the combined obstetrical services are Negro women. The ages of these women vary from 18 to 41 years, with an average of 27 (Table II). Eight of the patients were multiparas. It is of importance to note that 7 of the 10 patients did not have prenatal care. Many of our patients do not afford themselves of prenatal care. They routinely come to the hospital for the first time when they are either in active labor or in serious difficulty. The incidence of eclampsia on the Tulane service is approximately 1:911 deliveries.

Diagnosis

Of the 10 patients* reported on, 9 had severe pre-eclampsia (Table II) or eclampsia. One patient exhibited no signs or symptoms of toxemia. She developed pneumonia at the time of delivery, and retinal detachment was noted 5 days post partum. This case was the only postpartum retinal detachment in our series; it is included because

*All cases in this report will be presented in chronological order.

of the physical findings and the absence of trauma.

It is part of the "toxemia work-up" of the Tulane service, and the sister services, to dilate the pupils and examine the fundi of all patients with toxemia on admission to the delivery unit. The ophthalmology department is then consulted. The diagnosis in each instance was corroborated by an ophthalmologist. Only clearly established cases of retinal detachment are reported. If the ocular findings were at all doubtful, the patients were excluded from this series. The progress of all patients is then closely followed by both the obstetrical and the ophthalmology services.

Embryology, etiology and development

In the development of the eye, the optic vesicle (which is a hollow space) invaginates, so that the two sides lie together. The space that once existed disappears, leaving only a potential space or a "weak plane."[1] In the adult, this represents the site of apposition of the pigment epithelium to the layer of rods and cones. These layers will separate rather easily under pathological conditions. It is the separation of these layers that constitutes retinal detachment.

Most instances of retinal detachment are of the "idiopathic" or traumatic variety. In these patients, the condition will often become progressively worse if untreated and may even result in blindness of the affected eye. The majority of these patients must be treated surgically. In only a small percentage of retinal detachments, where there is pure "serous" detachment (such as is found in toxemia), is reattachment and recovery, as a rule, spontaneous.

The retinal changes in toxemia may vary from vasoconstriction of the vessels to gross areas of hemorrhage, exudates, massive edema, and finally retinal detachment. The origin of this subretinal edema is debatable.[2] Some claim it to be part of the generalized edema, while others ascribe its presence to spastic changes of the choroidal arterioles. (In 2 of our patients, gross edema was negligible.)

Ocular findings

The ocular findings in a large retinal detachment are characteristic and easily observable. However, the smaller detachments may escape detection. The area of the detachment is raised as compared to other areas of the fundus. This places the detached area in focus with a higher lens power than the rest of the fundus. The retina loses its pink color and appears dull and gray. It is often thrown into folds and has a wavy appearance. The retinal vessels may be seen to alter their course and appear black.

Signs and symptoms

Nine of the 10 women in this series were acutely ill upon admission. Seven had severe pre-eclampsia. Two were admitted with grand mal convulsive seizures and were unconscious. In all of these patients the blood pressure was markedly elevated, ranging between 170 and 270 systolic and 100 and 140 diastolic (Table II). Eight patients exhibited 2- or 3-plus edema and proteinuria. The diagnosis of retinal detachment was made on admission and was found to be bilateral in 7 patients.

The presenting symptoms on admission are given in their order of frequency in Fig. 1. All patients complained of blurred or decreased vision. This was often described as "a cloud coming over me," or a "veil over my eyes." One patient reported she awoke in the morning to find herself "blind." In no instance was trauma an etiological factor.

Seven patients complained of headache and scotoma for *more than one week prior to admission*. Two patients were admitted in coma. One patient complained of ocular pain.

Table I

	Incidence
Toxemia	1:6.6
Eclampsia	1:911
Retinal detachment	1:18,524

Table II

Case	Age (years)	Gravidity	Prenatal care	Blood pressure on admission	Edema	Urine albumin
1	18	1	Yes	170/140	4+	4+
2	23	4	Yes	100/60	0	0
3	38	11	No	200/140	3+	3+
4	20	2	No	220/140	3+	4+
5	33	4	No	210/130	2+	2+
6	28	7	No	250/130	2+	4+
7	41	1	No	180/94	2+	Trace
8	27	1	Yes	180/120	3+	3+
9	21	2	No	170/110	1+	3+
10	24	5	No	185/110	1+	4+

Treatment

All patients were put to bed on the delivery unit in the toxemia room. Sedation was accomplished with phenobarbital. The treatment of toxemia has certainly changed in some aspects in the last 21 years, and this change will be reflected in the management of some of these patients. Methods and drugs that were used routinely years ago are now virtually discarded. While most of these patients have received narcotics and sedatives in large or continued doses as active treatment for toxemia in the past, this mode of therapy is no longer employed on the Tulane delivery unit. In the last few years we have almost eliminated the use of respiratory depressant in toxemic patients. The "old standby" of morphine and barbiturates in heavy dosage has been replaced by closely supervised intravenous drips of antihypertensive agents. No morphine was given to the last 2 patients in our series; they were given antihypertensive drugs. Three patients received magnesium sulfate intramuscularly and intravenously (Fig. 2).

The eye care for all patients was identical. It consisted of eye rest, the use of an eye shield, and dilatation of the pupil with homatropine. The purpose of dilatation of the pupil is solely to enhance eye rest by discouraging accommodation. Therefore, any drug that causes pupillary constriction is contraindicated. This is another reason that morphine should not be used routinely in the treatment of toxemia. The first 8 patients in our series did receive morphine or meperidine on the basis of this routine therapy, but the last 2 patients did not receive morphine.

We have occasionally employed the use of sandbags alongside the head to remind the patient that motion is not desired. Immobilization in the recumbent position allows for the retina to "float back" into position as the toxic process subsides. Ambulation is permitted as the reattachment becomes complete.

Table III. Management of delivery

Normal spontaneous	4
Cesarean section	4
Induction of labor (use of bags)*	1
Medical induction	1
Postpartum sterilization	2

*Occurred in 1938.

Management of delivery

The maternal complications often predicated the mode of delivery. There were 3 patients with toxic abruptio placentae, and one patient had had a previous cesarean section. Four cesarean sections were performed (Table III). Four more patients were delivered spontaneously shortly after admission. One labor was induced by the use of intravenous oxytocin drip. It will be noted from Table V that one pregnancy was artificially terminated by the use of bags. It is only fair to mention that this was done in 1937 because of increasing severity of toxemia, inability to manage or control the toxemia, and progressive retinopathy. Not only did the detachment not improve, but

cotton wool exudates and other signs of nephritic retinopathy developed.

In each case it was considered proper to "empty the uterus" as soon as was feasible. The last 2 patients were given antihypertensive agents, but underwent cesarean section shortly after admission because of toxic abruptio placentae.

Results

Fetal. There were 6 live and 4 dead infants. Of the 10 infants, however, 7 were premature. There were 3 antepartal deaths and one intrapartal death.

Maternal. After delivery all patients improved. Signs and symptoms of acute toxemia subsided and vision returned. Gross vision was the first to return. Patients were first able to make out shapes and objects, and this was later followed by return of fine vision. Reattachment of the retina occurred in a time interval of 7 to 26 days with an average of 13 days needed after delivery for significant to complete reattachment. As will be noted in Fig. 3, the last 3 patients experienced complete reattachment in 10 and 7 days, respectively, probably reflecting improved toxemia therapy and more meticulous attention to the ocular management. Patient 2 was the only patient who did not have toxemia. Patient 4 was lost to follow-up after discharge from the hospital at which time reattachment was essentially complete.

Postpartal return of vision was excellent in 7 patients, good in 2 patients, and unknown in 1 because of failure of that patient to return to the clinic for follow-up. However, she was discharged with "good vision."

Two of these patients were later sterilized in order to prevent further ocular damage with subsequent pregnancies. One patient was readmitted 6 weeks later for a tubal ligation. Another patient was seen at her next pregnancy (which was uneventful) and a cesarean section hysterectomy performed. However, at least 2 other patients have had one or more subsequent normal pregnancies and deliveries with no further eye complaints or symptoms.

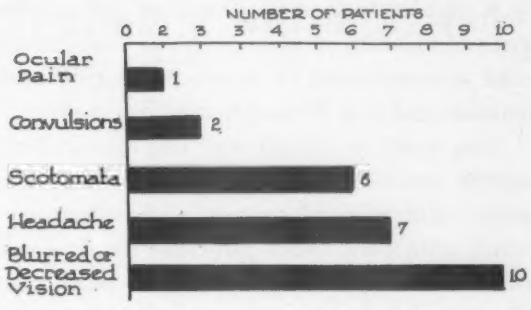

Fig. 1. Signs and symptoms on admission.

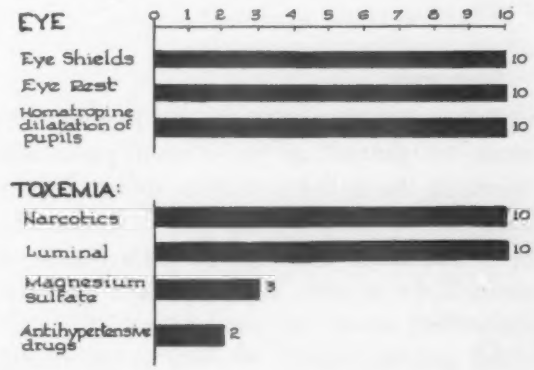

Fig. 2. Treatment.

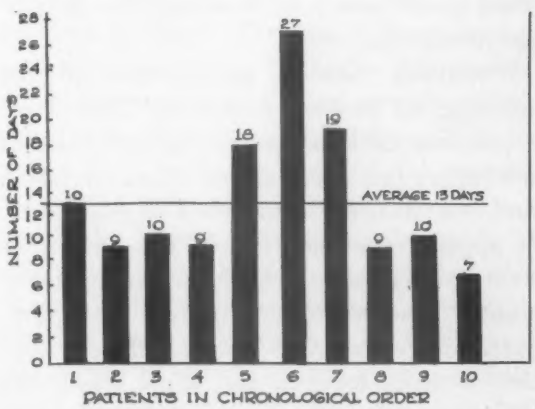

Fig. 3. Time for significant reattachment to occur post partum.

Complications

One patient developed a septic postoperative course, and a diagnosis of suppurative pelvic thrombophlebitis with suppurative pulmonary infarction was made. She was treated with ligation of the inferior vena cava and both ovarian veins. She responded dramatically and was discharged well with no residua.

A tracheotomy was necessary in another patient because of obstruction to respirations and accumulation of secretions during convulsive seizures. Recovery was uneventful.

Our most recent patient had particularly severe pre-eclampsia with a 50 per cent toxic abruptio placentae and subsequent renal shutdown. With judicious employment of intravenous fluids and careful regulation of electrolyte balance, she responded rapidly. Retinal reattachment was complete in 7 days.

There were no maternal deaths.

Summary

Ten cases of spontaneous retinal detachment in pregnancy have been presented. Seven of the patients had no prenatal care. Nine had severe pre-eclampsia or eclampsia. It is apparent that retinal detachment is more likely to occur in the patient with uncontrolled, severe toxemia.

All patients noted blurred or decreased vision. The majority complained of headache and scotoma for at least one week prior to admission. In 7 patients the detachment was bilateral.

Following delivery and control of the toxemia, all patients improved. There were 4 cesarean sections, four normal spontaneous deliveries, one medical induction of labor, and one artificial termination of pregnancy. It appears that delivery of the patient as soon as is feasible is still the treatment of choice. Whether or not the use of antihypertensive agents will permit sufficient control of acute toxemia and allow retinal reattachment to occur without delivery is a question that remains to be answered. Certainly, it seems that the use of antihypertensive agents post partum to more smoothly control the course of the patient is beneficial, as was reflected in early complete reattachment.

The return of vision was excellent in most of the women. The average time needed for spontaneous reattachment to occur was 13 days.

Two of the patients were later sterilized. However, at least 2 others have had one or more subsequent normal deliveries. With good prenatal care, postpartum sterilization is not necessary and has no rational place in treatment of this entity.

Conclusions

1. Retinal detachment is a rare complication of pregnancy. It occurs principally in the patient with uncontrolled, severe toxemia who has had no prenatal care.
2. Headache, scotoma, and blurred or decreased vision are symptoms worthy of careful consideration.
3. The retinal detachment is of the serous type and is most often bilateral.
4. Delivery of the patient as expeditiously as possible is still the treatment of choice.
5. Management of the toxemia, eye rest, and dilatation of the pupil compose the recommended adjunctive therapy.
6. Recovery is spontaneous and almost always complete after delivery. The average time for reattachment is 13 days.
7. Postpartum sterilization is not necessary if good prenatal care is made available to the patient with future pregnancies.

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Evaluation of a new cobalt chelate with iron in pregnancy anemia

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COBALT-IRON therapy has been widely used in the prevention and treatment of iron deficiency in pregnant women. Thorough evaluations have shown this combination to be more effective than the administration of iron compounds alone.[1-4] The discovery that cobalt exerts its erythropoietic action through the increased formation of an erythropoietic hormone, erythropoietin,[5, 6] has placed cobalt-iron therapy on a rational basis and provides a logical explanation of the superiority of the results obtained.

The therapeutic use of simple salts of heavy metals such as cobalt, however, is subject to the possible appearance of excessive concentration of heavy metal ions in the blood stream. Thus, rapid intravenous injection of cobaltous chloride produces, as is also the case with other heavy metal salts, a series of toxic symptoms grouped together as the "heavy metal effect."[7] The appearance of excessive temporary concentrations of cobalt ion in the blood after oral administration may, in fact, explain the occasional reports of cobalt toxicity and side effects which have appeared in the literature.[7-9]

The discovery that new types of metal complexes, the metal chelates, liberate their ions only under certain circumstances appears to offer interesting therapeutic possibilities in the use of metal therapy generally. Obviously, if a cobalt chelate could be prepared which would liberate cobalt ion only as needed by the rate of cellular metabolism, side effects and toxicity due to excess free cobalt ion would be minimized or eliminated.

We became interested for this reason in a new cobalt chelate, cobalt disodium ethylene bis-imino diacetate (Copoietin)* as a therapeutic agent. Copoietin liberates no detectable cobalt ions in solution in gastric juice or in blood samples, in vitro. Pharmacologically, both the acute and chronic toxicity of Copoietin in rats and rabbits is negligible. Whereas the toxic "heavy metal effect" appears promptly on administration of cobalt chloride intravenously, no reaction appears with Copoietin.[7] Approximately one eighth to one third of the dose administered is eliminated in the urine as cobalt ion.[10]

When assayed by the methods proposed by Goldwasser and associates,[5] Copoietin is effective in stimulating the formation of erythropoietin. Like cobalt chloride, it increases the hemopoietic indices in test animals.[7]

It would seem, therefore, that Copoietin is absorbed and transported as the bound

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*Furnished as Copoietin-ferrous by Lloyd Brothers, Inc., Cincinnati, Ohio.

metal chelate, liberating the metal ion only as utilized by the body tissues.

The efficacy of cobalt chloride–ferrous sulfate administration has been well established as an aid in the prevention and treatment of pregnancy anemia.[1-4]

This report presents clinical data obtained in a preliminary evaluation of cobalt disodium ethylene bisimino diacetate with ferrous sulfate for the same therapeutic indications.

Materials and methods

A series of 135 consecutive pregnant patients, appearing at the prenatal clinic, Creighton University Dispensary, Omaha, Nebraska, formed the patient material for this study. Patients who failed to take medication as directed and those who missed numerous appointments were excluded.

Patients showing evidence of megaloblastic or hemolytic anemia or those in the third trimester of their pregnancy were excluded from the study.

Each alternate patient included was given 4 daily doses either of 200 mg. each of exsiccated ferrous sulfate or of 100 mg. of exsiccated ferrous sulfate with 110 mg. of Copoietin.

The 53 patients who completed this study ranged in age from 15 to 43 years. The mean age was 22 years.

The medication was provided at regular clinic visits and careful check of the tablets unused at each visit was made in an effort to determine that the medication was actually taken as prescribed. Patients were also questioned at this time concerning side effects.

Treatment was begun in the majority of the cases in the second trimester of pregnancy at the time of the initial visit to the clinic. The average period of treatment of those receiving ferrous sulfate was 140 days; the average for those receiving Copoietin-ferrous was 155 days.

Hemoglobin and hematocrit determinations were chosen as the essential indices and were determined initially before therapy and one or more times at least 2 weeks prior to delivery. Postpartum determinations were done 4 to 8 weeks later.

Hemoglobin values were determined by Drabkin's cyanmethemoglobin method, using a photoelectric hemoglobinometer standardized with a 60.4 mg. per cent solution of cyanmethemoglobin at 540 mμ.

Hematocrit determinations were made by the usual microhematocrit procedure.

Bone marrow specimens were obtained by sternal puncture. Stainable iron was estimated in these specimens by the Prussian blue methods of Rath and Finch and of Dacie, and by the Turnbull blue method of Koszewski.[11] Differential counts of marrow cytology were made in the usual way. Marrow specimens were identified only by code when studied.

Routine urinalysis and quantitative serum bilirubin determinations (van den Bergh method) were done routinely in the Dispensary laboratory.

Results

Table I shows the results obtained in 35 patients receiving Copoietin-ferrous and in 18 patients receiving ferrous sulfate.

Comparison of the data in Table I indicates that the hemoglobin level was maintained or improved in approximately the same proportion of patients during pregnancy whether they received Copoietin-ferrous or ferrous sulfate in twice as great a dosage. However, the mean hemoglobin values for patients receiving ferrous sulfate showed no increase while those of patients receiving Copoietin-ferrous showed a mean increase of 0.7 Gm. per 100 c.c. representing 6.2 per cent of their initial hemoglobin value. Gastrointestinal intolerance was definitely less prominent with Copoietin-ferrous.

Three patients in the ferrous sulfate group did not follow the prescribed regimen. Dosage was reduced to 2 tablets daily in 2 of these because of gastrointestinal side effects. Two of the 3 did not maintain their initial hemoglobin status.

In the Copoietin-ferrous group, dosage was reduced to 2 tablets daily in 2 patients;

Table I. Comparative hematologic results with Copoietin-ferrous

	Copoietin-ferrous group (100 mg. $FeSO_4$ per dose)	*Ferrous sulfate group (200 mg. $FeSO_4$ per dose)*
No. of patients	35 (100%)	18 (100%)
Initial hemoglobin (mean)	11.3 Gm. per 100 c.c.	12.2 Gm. per 100 c.c.
Predelivery hemoglobin (mean)	12.0 Gm. per 100 c.c.	12.2 Gm. per 100 c.c.
Change in hemoglobin value	+0.7 Gm. per 100 c.c.	0
Initial MCHC (av.)	31.3	33.1
Predelivery MCHC (av.)	32.4	34.0
No. of days treated	155	140
No. of patients in whom the hemoglobin levels improved or was maintained	26 (74%)	14 (78%)
Postpartum determinations	6 patients	4 patients
Initial hemoglobin (av.)	10.8 Gm. per 100 c.c.	12.6 Gm. per 100 c.c.
Postpartum hemoglobin (av.)	12.9 Gm. per 100 c.c.	13.6 Gm. per 100 c.c.
Increase in hemoglobin value	2.1 Gm. per 100 c.c.	1.0 Gm. per 100 c.c.
Gastrointestinal intolerance	2 patients (6%)	3 patients (17%)

2 others took the medication only sporadically. Hemoglobin was maintained satisfactorily in only one of these 4 patients and, in this case, it was necessary to reduce the dosage only after 115 days of therapy.

The two series of patients described in Table I were not strictly comparable in terms of mean initial hemoglobin values. Accordingly, to aid in the interpretation of results, data were tabulated separately for the Copoietin-ferrous group and for the ferrous-sulfate group, using an arbitrary criterion of 12.0 Gm. per 100 c.c. hemoglobin, at the initial visit. Data are shown in Table II.

It is evident from Table II that Copoietin-ferrous and ferrous sulfate were of approximately equal effectiveness in maintaining hemoglobin values in patients whose initial hemoglobin levels were 12 Gm. per 100 c.c. or better and that Copoietin-ferrous produced significant increases in patients with initial values below this level.

Table III shows the results obtained in bone marrow examinations made before and near the end of therapy in 7 cases.

Three of the 4 patients receiving Copoietin-ferrous showed increases in stainable marrow iron; none of those receiving ferrous sulfate showed any detectable in-

Table II. Hematologic comparison based on initial hemoglobin values

	Copoietin-ferrous group		*Ferrous sulfate group*
	Initial value 12.0 Gm. per 100 c.c. or more	*Initial value below 12.0 Gm. per 100 c.c.*	*Initial value 12.0 Gm. per 100 c.c. or more*
No. of patients	13	22	16*
Initial hemoglobin (mean)	12.3 Gm. per 100 c.c.	11.0 Gm. per 100 c.c.	12.4 Gm. per 100 c.c.
Predelivery hemoglobin (mean)	12.0 Gm. per 100 c.c.	11.5 Gm. per 100 c.c.	12.2 Gm. per 100 c.c.
Initial MCHC (av.)	32.4	30.6	33.4
Predelivery MCHC (av.)	32.8	32.6	34.1
No. of patients showing no hemoglobin decrease	4	19	6
No. of patients with predelivery hemoglobin values of 13.0 Gm. per 100 c.c. or better	3	4	5

*The hemoglobin levels in 2 of the 18 patients in this group presented in Table I fell below the 12 Gm. per 100 c.c. level and these patients were excluded from that grouping in Table II.

Table III. Effect of treatment on reserve storage iron

Patient	Stainable marrow iron	
	Initial	Final
Copoietin-ferrous		
L. D.	1+	3+
C. S.	1+	2+
L. S.	1+	1+
O. M.	1+	2+
Ferrous sulfate		
E. E.	1+	1+
M. W.	2+	1+
B. A.	1+	1+

crease. No changes were observed in marrow cytology.

Neither the van den Bergh quantitative test nor routine urinalysis as performed in the Dispensary laboratory showed any evidence of abnormality which could be ascribed to patients receiving Copoietin-ferrous.

Comment

Our findings in patients who received ferrous sulfate are in good agreement with those of others who have reported that only about 80 per cent of pregnant women maintain or improve their hemoglobin even with the best iron supplementation.[1, 2]

A hemoglobin level of approximately 12 Gm. per 100 c.c. appears to represent a "normal" value for women[1, 12] and a point above which iron deficiency is seldom present.[13] Accordingly, we chose to compare the results in two groups of women with initial hemoglobin values of this order, who were receiving, respectively, Copoietin-ferrous and ferrous sulfate (Table II). Comparison of these data, considering the relatively few patients involved, indicate that Copoietin-ferrous was approximately as effective in maintaining hemoglobin values in hematologically normal women as was ferrous sulfate. This was true despite the fact that Copoietin-ferrous provided only one-half the quantity of iron given the group who received ferrous sulfate.

The majority of patients who received Copoietin-ferrous had either begun their pregnancy with hemoglobin levels below 12 Gm. per 100 c.c. or their index had fallen below this level at the time of their initial visit. It may be assumed, therefore, that iron reserves in this series were minimal when treatment was begun.[14] Since the average patient began treatment late in the second trimester, these patients were subject to heavy fetal requirement for iron at a time they were least able to supply this demand without a further loss of hemoglobin. It is in this type of situation that iron therapy is usually least effective since absorption often fails to keep pace with the iron requirement. Thus, only 4 to 5 mg. of elemental iron can be absorbed daily by the anemic patient. This is less than the optimal needs of the marrow and thus accounts for the developing deficiency.[13] In our series of such patients, however, excellent results were obtained with Copoietin-ferrous, despite the relatively low iron dosage (Table II). The mean hemoglobin values showed an increase and mean corpuscular hemoglobin concentration values rose significantly toward the normal. Nineteen of the 22 patients showed no further decrease in hemoglobin levels depite the physiologic dilution which becomes marked during this period. These results certainly indicate that the existing or developing iron deficiency in these patients was arrested and corrected by Copoietin-ferrous therapy.

On an over-all basis, 38 of our 53 patients (71 per cent) could be classified as iron deficient at the time of their initial visit. This probably reflects in part the lower economic status of the patient load at this clinic. In this group as a whole (Table I), patients receiving Copoietin-ferrous showed an increase in mean hemoglobin level and in mean corpuscular hemoglobin concentration values, thus indicating improvement in the iron status of these patients. Postpartum determinations suggest that women who received Copoietin-ferrous were in a better iron status than at the time of their initial visit when medication was begun. This does

not appear to be the usual result without suitable iron supplementation.[15]

It is generally recognized that the average woman is in a precarious state of iron balance and thus begins pregnancy with little or no reserve iron.[16, 17] Bone marrow studies lend added support to this concept.[14] The ideal aim of therapy would be not only the maintenance of the hemoglobin level throughout pregnancy but the simultaneous building of iron reserves. This has not proved possible with the usual iron therapy and it is widely recommended that iron be given for prolonged periods after parturition in an effort to build reserve iron.[13] Even this, however, has not proved to be effective on a practical basis.[18] There is a definite need, therefore, for an iron supplement which could not only maintain hemoglobin values but permit the increased iron absorption necessary to build iron reserves during pregnancy.

Stainable marrow iron, as an index of the patient's iron reserve, was estimated in 7 of our patients before and after treatment. As was expected,[14] no change was seen in the minimal initial findings in those receiving ferrous sulfate. An increase, however, was found in 3 of the 4 patients who received Copoietin-ferrous. Similar observations have been reported in patients receiving cobalt-iron compounds.[4, 19] These findings suggest that the administration of cobalt with iron increases the absorption of iron sufficiently to permit the building of iron reserves in the pregnant woman despite the heavy fetal demand. Cobalt increases the rate of erythropoiesis through increased erythropoietin formation[5, 7] and, since the rate of erythropoiesis is a determining factor in the rate of iron absorption, it appears logical to assume that this is the mechanism by which Copoietin may increase iron absorption in the pregnant woman.

Because of the importance of improving iron reserves in the female patient and the ineffectiveness of present iron therapy for this purpose, further studies of the effectiveness of Copoietin-ferrous in building iron reserves should be made.

No side effects, other than gastrointestinal irritation, were attributed to the medication in any patients in our series. Laboratory data gave no evidence of toxic effects in patients receiving Copoietin-ferrous. Gastrointestinal intolerance was less marked in the Copoietin-ferrous group, probably because of the lesser dosage of iron present in this medicament.

Summary

We have evaluated the clinical use of Copoietin-ferrous, a new chelated cobalt-iron complex, and ferrous sulfate in a series of 53 pregnant women.

In pregnant patients with no manifest iron deficiency, the new compound (Copoietin-ferrous) appeared to be fully as effective in maintaining hemoglobin levels as was ferrous sulfate in twice as great a dosage.

In pregnant patients in whom iron deficiency may be assumed to have been present, Copoietin-ferrous produced an improvement in the blood picture and the evidence suggests that it caused an increase in the reserve storage iron.

Side effects were limited to gastrointestinal intolerance and this was less marked with Copoietin-ferrous than was the case with ferrous sulfate.

Stainable marrow iron, as an index of reserve storage iron, was increased in pregnant patients receiving Copoietin-ferrous. These women, therefore, were better prepared for subsequent menstrual blood loss or future pregnancies.

Copoietin-ferrous appears to be an excellent hematinic for use in maintaining and improving the hemoglobin status of pregnant women.

Bone marrow studies were done by Dr. B. J. Koszewski, Department of Medicine, Creighton University School of Medicine.

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CURRENT OPINION

Pertinent comments

The statistical approach to the study of clinical phenomena

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IN ORDER to justify the expenditure of effort in pursuing a clinical study, the space it may occupy when ultimately published, and the intrusion on the reader's valuable time and thought processes, one should be prepared to demonstrate the relative merits of the material or techniques being investigated. Coupled with this is the ever-present and growing responsibility on the part of the medical journal, and more specifically, of its contributors, to convey information in an accurate and unbiased manner. "Formal statistical analysis is not an infallible guide to decision; it does not replace common sense, and it has little to do with creativity, imagination, and insight. It is a useful tool."[1] Bearing this in mind, we should nevertheless be alerted to the apparent truth that the many unperceived pitfalls which frequently ensnare the unwary in clinical experimentation make imperative the use of authoritatively critical tests of statistical probability and the adherence to basic principles of experimental design. Without these latter, the reported results of the best-conceived clinical investigation often stand ignobly indistinguishable in a quagmire of mediocrity.

The pitfalls referred to are numerous and often subtle. When not circumvented, they detract from the intrinsic value of any study. They include among others, biases of all types, data of poor quality, and subjectivity of responses, and are compounded by our frequent need to deal with self-limiting and remitting disorders.

Recognition of bias requires critical objectivity. It is exceedingly rare for any clinical study to be entirely devoid of some bias, and this may even apply to those constructed according to strict statistical design. It is well known, for example, that both alternate case selection and serialization (odd and even numbers) may be seriously biased modes of assignment and may fall quite short of true randomness in the statistical sense. It is only when completely equal opportunities are offered to every subject to be included in any of the treatment groups, so that no prejudicial direction is given by either the investigator or the patient, that bias in selection may be considered to be absent. This equality of opportunity is a fundamental prerequisite in applying the principles of chance, i.e., statistics, to research.

Even the use of controlled observations, unless these are truly comparable in all ways (except, of course, for the treatment

modalities), may not give an accurate picture of the problem. The so-called "double-blind" approach, usually an ideal arrangement, may at times not succeed in averting spurious conclusions. The lack or loss of randomization of case selection may give rise to groups of false controls, who may by their very make-up be preferentially responsive to any given treatment. Data obtained from these groups may be sufficiently misleading to permit the derivation of erroneous conclusions under the surveillance of even the most critical tests of statistical significance. That these tests are inapplicable where bias exists is usually unrecognized or ignored, thus compounding the misdeed.

Biases may appear in such forms as overt falsification (happily quite rare) or human errors in observing, recording, or reporting, and these may reflect blind enthusiasm or hypercritical nihilistic attitudes, as well as subconscious presupposition and self-suggestion. The loss of patients from a study, whether relevant to treatment effect or not, may introduce another major form of bias; if in sizable numbers or if unequally distributed among the groups, losses may entirely invalidate a study.

Poor data, which are imprecise and haphazardly or ineptly collected and recorded, are valueless and defeat the purpose of clinical experimentation. "No high-powered analysis of data will compensate for data of poor quality or dubious validity."[2] Differences detected between drugs or between a mode of treatment and a placebo are meaningless under these conditions; even if real and substantial differences actually exist, they may not be detectable. Precision, then, is paramount. In addition, terminology must be crystallized so that equivocation cannot arise; definitions must be clear; observations must be carried out uniformly and accurately, so that they are comparable throughout.

Many factors may contribute to the general penury of data including the use of coarse parameters of evaluation, ill-defined class of patients under study (inadequately defined disorder), insufficient numbers of patients available and tested, inadequate or improper sampling of available population, high incidence of losses, improper measurement of alleged therapeutic effect, and the absence of reference standards (drugs with recognized effect) for comparison.

Subjectivity of response is unavoidable in the evaluation of many clinical disorders, except for those where death or other objective phenomenon is an end point, or where changes in pertinent measurable features can be studied quantitatively. Since one of the primary aims of clinical medicine is the alleviation of subjective symptoms (in the course of finding and relieving the cause), the considerable effort expended in evaluating effectiveness of therapeutic agents is warranted. Mindful of the recognized unreliability of human judgment, however, one must act to avoid disastrously misleading enthusiasm by both investigators and subjects, engendered by inherent desires for success, and augmented by unconcealed awareness of the anticipated effect of the active therapeutic principle. The subtleties of such awareness may be reflected in innumerable possible ways to the detriment of honest evaluation.

The requirements for critically controlled evaluations encompass many obstetrical and gynecological conditions, most especially those manifest in whole or in part by subjective symptoms or whose pathognomy may largely be influenced by psychic overlay. Included also are evaluations of classes of medications used wholly or in part for their effect on subjective symptoms, such as analgesics, sedatives, hypnotics, antipruritics, and antiemetics. Qualitative estimations of effectiveness of these latter usually constitute mere clinical impressions, serving as series of testimonials, and are therefore not dependable as such.

Design of clinical studies

In order for clinical evaluations of this nature to attain significance, have real meaning, and avoid the pitfalls to which they are prey, certain essential safeguards should be incorporated into their design and conduct.

These time-proved ingredients for success include (1) true randomization, (2) use of placebos, (3) "double-blind" techniques, (4) comparisons with accepted standards of reference, (5) use of correlated data where feasible, (6) appropriate statistical validation, and (7) cautious and pertinent statement of conclusions or generalizations from the data. The first five of these involve basic disciplines in experimental design, without which the sixth could not be applied, and the seventh would be meaningless.

Detailed discussions of techniques involved in complying with these measures are beyond the scope of this presentation. Instead, illustrative examples are given to demonstrate the shortcomings of poorly designed studies. It will become quite clear that repairing the damage is not always possible, so that data gathered by diligence and considerable effort may have to be discarded in favor of a fresh start. In order to avoid this unfortunate and disheartening turn of events, one would do well to be duly forewarned.

Randomization. Randomization of case selection for the assignment of treatment modalities is one of the basic conditions required in setting up clinic studies. It implies true chance assignment, as in tossing a coin, so that intrinsic bias is minimized. It may be accomplished by many devices, including use of random number tables, random blocks, cross-over designs, and Latin squares (predetermined random arrangements of sequences). More popular (but often considerably less reliable) are alternation or serialization methods, the shortcomings of which are sometimes all too apparent. Large dividends in validity result from the small investment of effort required to devise systems of truly random assignments.

Illustrative examples of relevant invalid experiments include: (1) those without controls, in which a series of consecutive patients are treated for a given disorder and the results contrasted with published effective rates for other forms of treatment and incidence of spontaneous remission, if known; (2) those with nonrandom assignment of treatment and controls, as seen in alternate or consecutive series, wherein one group receives a treatment, the other none, and the two groups are compared analytically; and (3) those randomly assigned to drug and to control groups in a proper manner, but with full knowledge (by personnel, investigators, and even by patients) of which are receiving the active forms of therapy.

The first of these (no control) is entirely unsatisfactory with but rare exceptions, arising only in conditions where controls are untenable (e.g., fatal disorders). There are very few universally acceptable and applicable cure rates available for this type of clinical comparison. Other series of cases may be outwardly similar, but need not be comparable in important but subtle ways; they may be constituted of more severe cases; their nutritional status may have been poor; supportive care may have been inept; their emotional needs may have been ignored; indeed, their rates of spontaneous remission for that particular disorder, in that geographical area, at that season, in a group of that ethnic make-up may have been much lower. Innumerable factors, many not evident, may exist to account for any differences which may be encountered, other than that of the new treatment. Indeed, the very fact that a study is being done improves over-all patient care.

The second approach (nonrandom controlled series) occasionally suffices, but significant biases may be introduced unwittingly in case selection, in observation, and in interpretation and evaluation of treatment effect. Resulting errors are rarely deliberate, but in the absence of objectivity may arise readily and unperceived. Disturbances of the established sequence of patient assignment, for instance, may occur with justification in real or imagined reasons, either before or after assignment. In this and other less obvious ways the treated and untreated groups become dissimilar in composition as regards uncontrolled variables such as age, sex, race, nutritional and emotional status, severity of disease, etc. Clearly, these groups are not comparable and, therefore, need not

be expected to respond similarly with respect to treatment. If the treated patients were to fare better than their untreated confreres under these circumstances, one could not in all honesty and assurance ascribe this difference in response solely to therapy.

The third example (random series) effectively curbs bias due to patient selection (except perhaps for overt deception after allocation) by the very nature of the method whereby assignment is made on a predetermined completely arbitrary basis. If sufficient numbers of cases are included in each group all variables should ultimately equalize, so as to satisfy the basic requirement that the groups be really comparable. By these means, none of the spurious techniques for adjusting unit history numbers on admission or changing patient sequences prior to alternate selections will suffice (the extent of such guileful duplicity, while rare, may be surprising). Other less obvious biases, however, may appear because the responses and their evaluations are nonobjective. Where the patient is aware that she is not being actively treated, negative effects are to be expected; those who appreciate that they are receiving active and potentially effective therapy tend to respond in a positive manner, as a manifestation of both willful and subconscious desire to improve, to please the physician, and to conform. Hospital personnel, similarly aware, will influence the results by means of suggestive optimism, preferential care, and weighted evaluations of responses. Investigators, too, are not free of prejudicial judgment under the influence of this knowledge.

Placebos and "blindness." This brings up the inseparable factors of "blindness" in evaluation and the use of placebos. Because of the need to distinguish the pharmacological from the psychological effects of a drug, placebos have become an integral part of clinical experimentation. The study of the remarkable power of the placebo[3, 4] has revealed its effectiveness as a therapeutic measure in psychological illnesses, as a method for distinguishing drug effects from suggestion, and as a device for curtailing biases originating in both the patient and the observer. Using the placebo for treatment of the control group of patients averts the unpleasant clinical situation of apparent neglect, thus minimizing factors of suggestibility. In situations where the identity of active medications and placebos are unknown to patients, personnel, and investigators alike (double-blind) prejudicial influences become negligible, approaching the idealistic end result of preventing the inadvertent introduction of virtually all biases.

The use of the inactive placebo, or dummy, alleviates problems referable to subjective effects except in those instances where a definable action or side effect should be experienced. Such subjective effects, and these need not necessarily be those of the active drug being tested, may provide the psychological impetus necessary to produce a placebo effect which may be indistinguishable from the drug effect being sought. The perfect active placebo, which would mimic all side actions without having specific treatment action, is rarely available. The problem can attain considerable complexity and is producing varieties of triple-blind evaluations to determine differences, if any, between drug effect and that of both active and inactive placebos.

Examples involving these principles include: (1) the single-blind experiment, wherein patients are randomly assigned to treatment with active drug or identical placebo, and the group results compared statistically; and (2) the double-blind investigation, involving random allocation of drug and placebo, both administered as unknown substances.

As above described, the single-blind technique suffers largely from the potential bias which the investigator himself may unwittingly contribute by presupposition, whether enthusiastically pro or con. It is a great improvement over the previous example in which the patient is cognizant of the situation, but not nearly so effective as the double-blind approach of the next example, wherein the identities of drug and placebo

are also unknown to the investigator and other personnel.

The latter, although ideally both double-blind and random in distribution, may occasionally fall short of adequate evaluation. Absence of side effects which the patients and observers may expect (e.g., drowsiness, lethargy, dizziness, and other known non-analgesic actions in association with the evaluation of an anodyne for the relief of pain) reveals the obvious identity of the inactive placebo, and thereby effectively vitiates the guise of blindness. Where possible, incorporating a group treated with active placebo would strengthen this type of study. Where not possible, as is so often the case, random coding of all material (with placebo and active drug in more than one concentration, all identical in outward appearance and identified only by individual code numbers) may interfere sufficiently with easy recognition of the dummy medication to avert this problem.

Reference standards and correlated data. Beyond this point, the niceties of statistical design may appear to be unnecessary embellishments, except in so far as they offer means for more critical appraisal. Among others, these include the basic concepts of reference standards and the use of correlated data. In order to be able to demonstrate the relative merits of the drug or method under surveillance, it should be shown to be significantly different in effect from the placebo and at least as good as (and preferably better than) a standard accepted preparation (i.e., the reference standard) already in wide use and of proved value. Advantage may be found in demonstrating curtailment of deleterious or annoying side effects which the standard drug may present, without necessarily showing any superiority in drug effect. This then would justify the presentation of a clinical study which compares new and old treatment modalities (and placebo) with reference to both symptom relief and side actions.

Considerable difficulty may arise with reference to dosage and interval and duration of administration and, unless dose-response relationships (as well as toxicological studies) have been detailed before the study is initiated, can severely jeopardize its validity. Where average effective doses are known, dose-response relationships may be elucidated clinically by using two or more dosage levels of the drug being evaluated and of the standard for comparison. The task of assaying the responses of large numbers of individuals treated with one of several separate medications, however, may appear monumental. The burden may be reduced by successive administration of all the products to each individual patient. This technique (correlated data) eliminates the need for extensive series, each patient in effect acting as her own control.

Certain additional precautions, however, become important. Since temporal relationships may be pertinent (as regards cyclical or progressive spontaneous abatement of the symptom complex, cumulative effects of medications, mutual potentiation, synergism, inhibition or interaction of drugs, and possibly unrecognized prolonged action which would reflect falsely on the benefits of a medication given subsequently) the assignment of drug order must be such as to permit none to have the advantage. Random methods of assignment (such as the Latin square type of distribution, for example) are available to accomplish this end. The additional difficulty in analysis of data acquired by these techniques is well counterbalanced by the savings in size of series needed and, of greater importance, by the reduction of sampling biases. This latter is the result of each patient serving as her own control and theoretically remaining essentially unchanged as each successive medication is administered.

Other techniques of matching or pairing, wherein cases are matched with all due care as to as many variable factors as feasible (such as age, race, sex, economic and nutritional status, etc.) thereby to create two nearly identical groups, offer similar advantages. These are useful in situations where it is not possible to administer more than one medication or technique of therapy to a given patient for a given illness (as

in disorders treated surgically or in those of short duration).

The principles enumerated above may be succinctly summarized in idealized examples of clinical studies involving evaluation of drug effect, as follows: (1) five randomly selected groups are treated with (a) single and (b) double dose schedules of the drug being tested, (c) single and (d) double strengths of known effective drug (reference standard), and (e) placebo, respectively; all preparations are physically identical, individually coded, and given as unknowns; (2) the entire series of treatments as described is applied in predetermined random order (Latin square) to each individual of a much smaller series.

Analytic methods. The facets of statistical design are innumerable and ramify widely. It should be made clear, nevertheless, that the analytic methods used to test the significance of data depend squarely on the design of the experiment by which these data were derived. All tests of significance attempt to determine the probability that differences found between two or more samples, drawn at random from a uniform population, might have occurred by chance alone. If this probability is sufficiently small (set by arbitrary convention variously at less than 1 or 2 per cent chance occurrence and still lower for situations of utmost gravity), one may be justified in concluding that the difference was influenced by factors acting unequally in the groups studied. The design of the investigation attempts to insure that all factors are held constant, maintaining the populations uniform, so that the statistical tests may be applicable.

It is not within the scope of this presentation to delve into the theory or techniques of statistical analysis. The choice of test depends on many factors, such as independence or correlation of individual datum and whether it is expressed in qualitative or quantitative terms. The simplest forms of analyses should be familiar to the active investigator, including analysis of variance by the generally applicable Fisher's "F" or "z" function, its important special modifications, Student's "t" and Pearson's chi-square, as well as the useful but less critical binomial distribution methods. The limitations of applicability of these techniques should be known. Where economy of numbers is a consideration, one may have to resort to the newer analytic methods of sequential analysis which may be carried out while the experiment is in progress. These allow for termination of the project at precisely the moment that sufficient data are available to support or refute a proposed hypothesis at a predetermined arbitrary level of statistical significance. The urgent need for prompt cessation of a trial of a new treatment method (particularly if it is ineffectual) is obvious in many phases of clinical work.

The clinical study which neglects to include statistical "proof" of stated contentions bears a major shortcoming and infers error by omission, just as an improperly performed analysis (by an inapplicable test, for example) reflects possible basic lack of understanding in design, performance, and analysis of the experiment. The use of the unadorned percentage (of cure, arrest, or amelioration), with its deeply ingrained basis in custom and usage, has little or no value without accompanying statistical evaluation. This is especially apparent in conditions which have high incidences of spontaneous remission or improvement, in series of small size, and in disorders in which large variations in responsiveness may be expected to be seen with and without treatment. In general, therefore, the use of percentages alone is to be deplored.

Cautious statement of conclusions. One is empowered to present as bona fide conclusions only that which has been demonstrated to be so within set limits of probability. One may, of course, state unproved hypotheses and even present tenuous observations, provided these are stated as such and in a manner which cannot be otherwise interpreted. The latter may be satisfactorily accomplished by a statement of the probability of the chance occurrence as determined statistically. In addition, the limita-

tions imposed by the conditions of the study must be clearly noted with reference to type, route, duration and dosage of treatment used, the precise class of patient material treated, and any other qualifying conditions which prevail.

Care must be taken in transferring the information obtained on a small sampling to a larger population. Perhaps such generalizations should best be avoided, at least until similar studies have added verification under different conditions of experimentation, so as to nullify possible ethnic and geographic influences, among others.

Statements of results obtained should conclude logically from the data and analysis. This discussion began with a statement that statistical analysis is not a guide to decision or a replacement for common sense and sound judgment. The obvious truism that illogical deductions are unacceptable is all too frequently ignored. A common example of misinterpretation occurs in association with the finding of differences which are not statistically significant. This implies only that the groups compared are essentially the same within the limits established, any differences found having occurred by chance; it has no bearing at all on the corollary statement that the groups could not possibly be different. More succinctly, if it is *not proved* that A is different from B (A group treated, B control), one cannot conclude that it is demonstrated that A could not be different from B, or that A could not be made to be different from B under other circumstances than the limitations imposed by the experiment. This type of error ("error of the second order" as differentiated from an "error of the first order" in which significant difference is alleged to exist when it does not) assumes incorrectly that failure to prove a difference between results is proof that no difference actually exists; this is seen frequently.

There are many other types of unsound and fallacious constructions including anachronistic assumptions of causal relationships between temporally associated events (both possibly affected by or the result of a third condition), and events which follow closely upon the administration of a treatment (and are, of course, attributed to the treatment in a *post hoc, ergo propter hoc* premise). Most are not always readily apparent. It may, therefore, be wise for the clinical investigator to seek the advice and counsel of the unprejudiced and disinterested statistician who is competent in these matters. He may provide the comfort and assurance of a well-thought-out study set up in advance with economy of time, effort, and finances in mind. He can be of inestimable aid in foreseeing the pitfalls described herein as well as innumerable others and in applying statistical techniques of experimental design and analysis to avoid them.

Conclusion

This presentation has attempted to highlight the hazards encountered in the evolution of a clinical investigation, to illustrate some of the instances in which these may be seen, to explain why they deserve emphasis, and to show some of the methods commonly used to circumvent them. If in doing this I have made the prospective contributor a bit more wary and the casual reader a bit more critical I feel the effort to be well rewarded.

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Superfetation

Report of a case and proposed method of radiological diagnosis

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IN A review of the obstetrical literature and texts no medically substantiated case of superfetation can be found. The delivery of multiple pregnancy where two separate ova are involved, the second conception occurring sometime after the first has developed, is an interesting phenomenon alluded to in the literature and substantiated only in lower animals. Ross[1] reported a case that comes closest to true confirmation of superfetation, but his case is in doubt as to proof. Studdiford[2] claims there is no proved case in humans and states that it is unlikely due to inhibition of ovulation with pregnancy. The present comment is primarily an attempt to suggest a new method of diagnosis of this phenomenon.

M. T., a 29-year-old para 3-0-1-3 with an essentially uneventful previous obstetrical history, had previous children weighing 6 pounds, 11 ounces; 7 pounds, 3 ounces; and 7 pounds, 13½ ounces at birth. The date of confinement was calculated as late January, 1960, and she was admitted in active labor with a twin pregnancy Feb. 8, 1960. The first twin, a male weighing 4 pounds, 10¾ ounces, was born at 8:11 P.M. The second twin was born at 8:16 P.M.; it was also a male and it weighed 6 pounds, 12½ ounces. Manual removal of the placenta revealed two separate placentas, one with a right cornual fundal implantation, the other implanted on the midposterior wall. Microscopic examination of the membranes revealed this to be a double ovum pregnancy with two amnions and chorions present.

Because of the great disparity in the size of these twins and the appearance of one as definitely clinically premature, the other apparently a full-term infant, it was felt that this might possibly represent a case of superfetation.

In an attempt to prove this diagnosis, x-ray films were obtained (Figs. 1 and 2). Twin A, the first delivered, weighing 4 pounds, 10¾ ounces, showed no distal femoral epiphysis, whereas Twin B showed a well-formed distal femoral and proximal tibial epiphysis.

Fig. 1. Twin A.

From the Obstetrical Service, Sinai Hospital of Baltimore.

Fig. 2. Twin B.

As is seen from Figs. 1 and 2, there is what would seem to be a disparity in bone age in these simultaneously delivered twins and it is felt that this may interestingly represent a method of proving the diagnosis of superfetation. Essentially this comment is in the form of a preliminary report in the hope that it will interest others to utilize this diagnostic tool perhaps on a routine basis. The only true proof would be a control series of twins to see if there is any disparity in bone age in simultaneously delivered twins that do not represent superfetation. If in normally delivered twins with no disparity in size and no question of disparity in gestational age the bone age appearance on x-ray is invariably identical, this would be a valuable diagnostic tool.

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Reviews | Abstracts

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Selected abstracts

Acta Cytologica

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*Papanicolaou, G. N., and Maddi, F. V.: Diagnostic Value of Cells of Endometrial and Ovarian Origin in Human Tissue Cultures, p. 1.

*Reagan, J. W., Bell, B. A., Neuman, J. L., Scott, R. B., and Patton, S. F.: Dysplasia in the Uterine Cervix During Pregnancy: An Analytical Study of Cells, p. 17.

Papanicolaou and Maddi: Diagnostic Value of Cells of Endometrial and Ovarian Origin in Human Tissue Cultures, p. 1.

The authors studied 50 cases of pathologically proved adenocarcinoma of the endometrium and 25 cases of peritoneal and pleural effusions, all washings, from proved adenocarcinoma of the ovary using tissue culture methods. The material consisted of human endometrial tissue obtained by aspiration, curettage, or hysterectomy and of peritoneal fluid or washings aspirated during surgical procedures. They used two techniques for the preparation of the cultures, the Maximow and the roller tube method. It was the opinion of the authors that the Maximow culture proved to be of greater value in the over-all study of the malignant endometrial cytology and of the prevailing growth patterns.

Observations on the morphologic characteristics and growth activity of the cells were made in living as well as in fixed and stained preparations. The malignant cells exhibited very active growth and an intense phagocytic activity. It was found that the cytological criteria of malignancy were comparable to those accepted in the pathology and cytology laboratories.

It is the belief of the authors that the tissue culture method can be most profitably used in obscure diagnostic cases in which the presence of a malignant neoplasm could not be established by any other diagnostic procedure. It also proved to be of great value in the detection of early cancer and in the evaluation of postradiation changes by ascertaining the viability of malignant cells which had been exposed to irradiation.

Good growth, particularly using the roller tube culture method, was observed within 16 to 24 hours and simple aspiration specimens can be obtained with relative ease in the majority of cases. It is felt that the tissue culture method may be employed, at least in certain organs, to greater advantage as an adjunct to other diagnostic procedures.

J. Edward Hall

Reagan et al.: Dysplasia in the Uterine Cervix During Pregnancy, p. 17.

The authors studied the cytologic material obtained from the cervices of 30 pregnant women. Of these, 6.2 per cent showed some degree of cellular abnormality, and 3 per cent showed cellular evidence of dysplasia which was subsequently confirmed by histopathologic study.

Cellular abnormalities were more common with increasing parity. The cellular studies from those with dysplasia contained a variable number of altered cell forms. Isodiametric forms were more common, accounting for 66.4 per cent of the cells. The cytoplasmic staining was cyanophilic in 82.0 per cent of the cells. The average nucleoplasmic index was 0.18. The nucleus was usually round or oval in form with a finely granular structure in 90.4 per cent of the cells, a coarsely granular structure in 3.7 per cent,

*These articles have been abstracted.

and constituting a translucent or opaque mass in 5.9 per cent of the cells.

Cellular changes reflected the structure of the lesions of origin varying in relation to the stage of pregnancy and the type of reaction which was predominant. Fourteen of the 28 women with dysplasia did not have cellular evidence of a change in the postpartum period. Of the 14 patients with demonstrable changes in the postpartum period 5 subsequently had negative studies, 6 had persistence of the lesion for varying periods, 2 were subsequently proved to have carcinoma in situ, and 1 was lost to follow-up.

There was no significant correlation between morphology in the initial specimen and the outcome. In general, however, there were more abnormal cells in the initial samples from women having lesions which were evident in the postpartum period.

J. Edward Hall

American Journal of Medicine

Vol. 30, February, 1961.

*Pollak, V. E., and Kark, R. M.: The Toxemias of Pregnancy and the Renal Lesion of Pre-eclampsia, p. 181.

Pollak and Kark: Toxemias of Pregnancy and Renal Lesion of Pre-eclampsia, p. 181. Renal biopsies were performed in 50 patients with toxemia of pregnancy, and exact histologic diagnoses were made. Ten patients had evidence of hypertensive vascular changes in the kidneys, and primary renal disease was found in 5. The characteristic lesions of pre-eclampsia found in the remaining 35 patients are described as showing widespread enlargement, swelling, and ischemia of the glomeruli. The most prominent pathologic lesion was cellular edema, affecting both endothelial and epithelial types, the former more than the latter. These changes were confirmed by electron microscopy. Repeat renal biopsies post partum showed normal glomerular structure.

Eight of the 35 patients with histologic evidence of pre-eclamptic glomerular lesions also had histologic evidence of underlying arteriolosclerosis and hypertensive vascular disease. The typical lesion of pre-eclampsia showed postpartum resolution, while the intrinsic vascular lesions persisted.

An attempt was made to establish clinicopathologic correlation between clinical and laboratory findings and tissue structure. In patients not treated with chlorothiazide derivatives, the levels of diastolic and systolic blood pressure, changes in hematologic constants, levels of serum electrolytes and nitrogenous substances, and degree of proteinuria, among other measurements, did not appear to be useful diagnostic indices of pre-eclampsia. Only the level of serum uric acid and the presence of spasm of the retinal vessels appeared to be helpful.

In a control group of 30 healthy pregnant women the serum uric acid level was 3.57 ± 0.69 mg. per 100 ml. Similar values were recorded for patients with hypertensive vascular disease. In the 35 patients in whom the diagnosis of pre-eclampsia was made on the basis of renal biopsy specimens, the serum uric acid level was 6.43 ± 1.74 mg. per 100 ml. The difference was considered highly significant. In 83 per cent of patients with pre-eclamptic lesions the uric acid level was elevated above the upper limits of normal for the third trimester of a healthy pregnancy; however, it was elevated in only 20 per cent of patients with hypertensive vascular disease. The significance of the elevated uric acid in pre-eclampsia is not clearly understood.

Thirty of the 35 patients with renal pre-eclamptic lesions were found to have retinal arteriolar spasm, and the degree of spasm was found to be a rough indicator of the underlying pre-eclamptic glomerular lesion. In patients with hypertensive vascular disease, very slight arteriolar spasm was found in two, and sclerosis of the retinal arterioles was found in 6 of them.

In a few patients with the most severe pre-eclamptic lesions the authors have observed, in addition to glomerular lesions, edema and swelling of the walls of arterioles, and small vessels were evident. Although neither fibrosis nor sclerotic vascular lesions were seen on examination of the initial biopsy specimen, there were definite vascular changes in the postpartum specimen. Arterioles and small arteries were no longer swollen but had become sclerotic. Similarly, although glomerular edema and ischemia had disappeared, distinct vascular changes in the root of the glomerular tuft were observed.

Harrison H. Sheld

British Medical Journal

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*Bruk, I., Dancaster, C. P., and Jackson, W. P. U.: Granulosa Cell Tumors Causing Precocious Puberty, p. 26.

Bruk, Dancaster, and Jackson: Granulosa Cell Tumors Causing Precocious Puberty. p. 26.

The authors report on 3 cases of precocious puberty caused by granulosa cell tumors in 2 of which both urinary and tumor estrogens were fractionated and assayed biochemically.

They found a good correlation between the severity of the clinical findings and the level of total estrogen secretion in Cases 1 and 2. The first patient, though younger, had more advanced pubertal changes than the second, and histology of the tumor showed more active mitosis. The excretion of both estradiol and estrone was higher in Case 1 than in Case 2.

The level of total urinary estrogens and the individual fractions was no higher than normally found in adult women in midcycle—in fact, not as high. Urinary gonadotropins (FSH) were raised to within adult range in both cases, with a fall in the level after operation in the one case in which it was measured postoperatively. Urinary 17-ketosteroid and hydroxycorticoid levels were normal.

The authors feel that the low levels obtained with their chemical methods suggest a deficiency in their techniques, in that they are possibly missing a potent estrogen fraction produced by the tumor not measured by the authors and that the raised FSH levels suggest the possible production of a gonadotropin substance by the tumor.

Stuart O. Silverberg

Cancer

Vol. 13, July-August, 1960.

*Christopherson, W. M., and Parker, J. E.: A Study of the Relative Frequency of Carcinoma of the Cervix in the Negro, p. 711.

*Fidler, H. K., and Boyd, J. R.: Occult Invasive Squamous Carcinoma of the Cervix, p. 764.

*Clark, D. G., Zumoff, B., Brunschwig, A., and Hellman, Leon: Preferential Uptake of Phosphate by Premalignant and Malignant lesions of the Vulva, p. 775.

*George, P. D., Fortner, J. G., and Pack, G. T.: Melanoma With Pregnancy, p. 854.

Christopherson and Parker: Relative Frequency of Carcinoma of the Cervix in the Negro, p. 711.

A predilection for carcinoma of the cervix to attack the Negro has been often implied in the literature. In an attempt to investigate possible reasons for this apparent racial selectivity, 10,045 women from a similar socioeconomic group were compared as to race and incidence of carcinoma of the cervix and cervical atypia.

The relative frequency of squamous carcinoma in Negro women in this series was no greater than that in Caucasian women. Parity was roughly equal in both racial groups, although the average age of first pregnancy was a year earlier in the Negro women.

The authors conclude that the reported higher frequency of cervical cancer in Negro women is not the result of racial susceptibility, but is associated with the lower socioeconomic status of the Negro in the United States.

Carl J. Pauerstein

Fidler and Boyd: Occult Invasive Squamous Carcinoma of the Cervix, p. 764.

The authors have presented 20 cases of occult invasive squamous carcinoma of the cervix discovered by initial or repeat examination of 80,000 women. A total of 700 cases of invasive squamous carcinoma of the cervix were found, with 20 cases meeting the criteria for a diagnosis of "occult hidden carcinoma."

The criteria used for a diagnosis of occult invasive squamous carcinoma of the cervix were: (a) that the cervix showed no lesion that could be biopsied, (b) that the cervical biopsy was negative, or (c) that a tissue diagnosis of intraepithelial carcinoma inconclusive for the presence of invasion, was obtained.

Sixteen of the patients were symptomatic with contact spotting, menometrorrhagia, and postmenopausal bleeding as the most frequent symptoms found. Four patients were asymptomatic. Significant physical findings were absent in 5 cases, cervical erosion was noted in 14, and leukoplasia in 1; 3 cases occurred in cervical stumps.

The methods used in diagnosis included cytology and biopsy. The cytologic findings were positive in 11 cases and suspicious in 7. In order to reach a definitive diagnosis, 14 patients had a cold knife cone biopsy of the cervix, 2 had a cervical stump removed, and 2 had simple hysterectomy. The final 2 cases in the series had lesions that conformed to the clinical definition of occult carcinoma and because adequate tissue was available for study, they were included.

Treatment was primarily intracavitary radium

(11 cases), with external radiation (4 cases) where lymphatic extension existed. Radical hysterectomy was done in 2 cases. The authors feel that proper treatment should be individually assessed, however.

The results of the study are not conclusive. Six patients are free of disease at 5 years. Two are dead, with one having died from carcinoma of the breast. Both patients who died were known to have lymphatic extension of the disease.

Four pathologic patterns were established. Group I showed extensive intraepithelial carcinoma with microinvasive foci and confluent invasion. There were 10 cases in this group.

Group II showed intraepithelial carcinoma with the origin of confluent invasive foci from deep gland extension without involvement of the surface mucosa. There were 4 cases in this group.

Group III revealed frank invasion from the portio vaginalis.

Group IV showed invasive carcinoma with minimal intraepithelial carcinoma in 4 cases. These were thought to represent a rapidly growing tumor or one that had destroyed the intraepithelial stages of the disease.

In summary, 20 cases of occult squamous carcinoma of the cervix were discovered, mainly by cone biopsy, exhaustively studied, and the lesions reconstructed. Four histologic patterns were established, the most common one being intraepithelial carcinoma with deep extension into the mucous glands showing scattered discrete foci of microinvasive regions of confluent, frankly invasive carcinoma.

The study appears to strengthen the concept that the natural history of carcinoma of the cervix is through several progressive stages.

Christopher C. Dotson

Clark et al.: Preferential Uptake of Phosphate by Premalignant and Malignant Lesions of Vulva, p. 775.

Thirteen patients with vulvar lesions ranging histologically from inflammation to frank carcinoma were given intravenous P^{32} based on the premise that hyperconcentration of phosphate is one of the characteristics of neoplastic cells. One to 3 hours later, radioactivity of the various diseased areas of the vulva and the comparable normal areas were determined. The results were expressed as ratio of counting rate for the normal tissue to counting rate for the abnormal tissue.

The lesions diagnosed as inflammation and radionecrosis displayed counts similar to normal skin areas. Kraurosis and leukoplakia yielded counts from 1.5 to 2.4 times the normal mean, and all points fell outside the normal range. The borders of leukoplakic areas could be sharply demarcated by the counter. Squamous carcinoma in situ yielded a range of 1.9 to 3.0 times the normal mean. In invasive squamous carcinoma the P^{32} uptake ranged between 2.4 and 6.9 times the normal mean. The range for carcinoma in situ thus overlapped both leukoplakia and invasive carcinoma. Lichen sclerosus et atrophicus falls into the same range as leukoplakia, and basal cell carcinoma into that of squamous carcinoma. On this basis perhaps lichen sclerosus et atrophicus should be considered a premalignant lesion. One such lesion in which carcinoma appeared is noted.

Carl J. Pauerstein

George, Fortner, and Pack: Melanoma With Pregnancy, p. 854.

One hundred and fifteen patients in whom melanoma and pregnancy coincided were compared with 330 patients who were not pregnant during the clinical course of the melanoma. Half of these patients corresponded in age to the study group.

The incidence of melanoma was highest in the 31 to 35 year group. Pregnancy and melanoma were most commonly associated in the 21 to 35 year age group.

The group with melanomas associated with pregnancy demonstrated a higher incidence of regional lymph node involvement than did the controls. There was no evidence of increased generalized metastases or of regional spread in the study group. The percentage of annual deaths was equal in the control and study groups, as was the total 5 and 10 year survival rate.

Pregnancy apparently does not exert any markedly adverse effect on the clinical course of melanoma.

Carl J. Pauerstein

International Journal of Fertility

Vol. 5, July-September, 1960.

*Moore-White, M.: Evaluation of Tubal Plastic Operations, p. 237.

Decker, A.: Transvaginal Diagnosis of Pelvic Disease, p. 251.

Nunez, A. C.: Pseudo-sterility and Infertility, p. 269.

Payne, S., and Stewart, W.: Fetal Abnormalities in an Infertility Practice, p. 273.

*Rozin, Samuel: The Roentgenologic Syndrome of Uterine Tuberculosis, p. 281.

Feldman, H. J.: Hysterosalpingography for Therapy With Infertility, p. 289.

Botella-Llusia, J., and Ruiz-Velasco, V.: Postcoital Test in Vitro, p. 301.

Bartlett, D. E., and Elliott, F. I.: The Constancy of Fertility of "Normal" Bulls as Expressed in Artificial Insemination, p. 307.

Schellen, Ton M. C. M.: The Cergical Spoon for the Diagnosis of Sterility, p. 311.

Laschet, U., and Weise, W.: Effect of Vitamin A on Animal Fertility, p. 317.

Moore-White: Evaluation of Tubal Plastic Operations, p. 237.

The author presents her results of 83 tubal operations which were divided into four main groups: salpingolysis 15, salpingoplasty (salpingostomy) 38, tubal implantation 16, and tortuous infantile tubes 14. The preoperative diagnosis was made by the studied interpretation of salpingograms. No case with ampullary stenosis or irregular filling with opaque medium was suitable. However, the results from specific numbers or types of preoperative diagnostic tests were not given. No mention was made of culdoscopy.

The type of operation involved 15 cases of pure lysis of adhesions accompanied in most cases by plication of the round ligaments. Follow-up of these patients revealed 14 conceptions, an enviable record.

For this group the author suggests that postoperative tubal insufflations be performed on the tenth postoperative day followed by one after the first menstruation. Dr. Moore reported 13 cases of pure bilateral salpingoplasty (salpingostomy) with or without lysis of adhesions. These were followed by 11 instances of tubal patency and 6 conceptions. Of the 14 pure bilateral implantation operations there were 9 patients who postoperatively had tubal patency and 8 of them conceived within 1 year except for 1 case. Histologic study of the resected tubes disclosed bilateral occlusive fibrosis with or without salpingitis isthmica nodosa in each case. Neither polyethylene nor antibiotics nor a reamer was employed in any of the cases. These results with histologically proved occluded tubes are superb.

The last section of this paper deals with the convoluted infantile tube the diagnosis of which is made by tubal patency in the absence of oscillations and/or the beaded appearance of the tube with poor spill of radiopaque material on salpingography. The author had 14 cases which were operated upon. At laparotomy the tube appeared to be convoluted because of a short mesosalpinx. The operation involved injection of air retrograde through the fimbriated end of the tube. Histologic section of 1 tube revealed a "structurally deficient and underdeveloped musculature." The results were 11 conceptions, 7 of which occurred 7 months or less after laparotomy. Dr. Moore attributes the splendid results to a dilatation of the thin-walled lumen and reduction of the number of kinks. There were no other stigmas of genital hypoplasia in the patients who had infantile oviducts.

Alvin M. Siegler

Rozin: Roentgenologic Syndrome of Uterine Tuberculosis, p. 281.

An analysis was made of 33 hysterograms which disclosed characteristic dwarfed shriveled and deformed uterine cavities with disproportionately long cervices. In some cases there was penetration of the iodized oil (Lipiodol) into the lymphatic vessels. In In 16 cases the tuberculous etiology was confirmed by histologic examination of the endometrium. However, in 11 cases it was presumed because of the presence of calcification of the pelvic glands with or without calcification of the ovaries and tubal stones. In 6 instances the presumptive evidence was based on a history of pulmonary and peritoneal tuberculosis. Hysterography is a valuable adjunct to aid in the diagnosis of genital tuberculosis.

Alvin M. Siegler

Irish Journal of Medical Science

No. 418, October, 1960.

*Elyan, Michael: Mongolism, p. 460.

Elyan: Mongolism, p. 460.

On the basis of publications by others, it is estimated that 7 to 10 per cent of all institutionalized mentally defective patients are Mongoloids. Moreover, with modern antibiotics, four times as many Mongoloids survive until the age of 10 years today as survived in 1929.

It has been widely accepted that in the Mongoloid the defect occurs between the sixth and eighth weeks of gestation. The mother who gives

birth to a Mongoloid child is approximately 10 years older than the average childbearing woman, but nevertheless the hypothesis that Mongolism is due solely to the exhaustion of products of reproduction cannot be substantiated, for Mongoloid children are sometimes born to young, healthy parents.

It has recently been established that the Mongoloid has 47 chromosomes instead of the usual 46.

When Mongolism occurs in twins, it is almost always in identical twins and it very rarely appears in nonidentical twins.

The problem of diagnosing Mongolism in infancy frequently presents difficulty. Some of the classical signs are often absent. An x-ray investigation of the pelvis of 36 Mongoloids showed a varying degree of pelvic deformity in every case. The outstanding features were: greatly reduced acetabular angles which were 14 degrees or much reduced below this angle and universally increased iliac angles. Bilateral valgus deformity of the femoral necks was present in 89 per cent of the younger group investigated.

Many treatments have been tried, including the administration of various hormones, but none have proved effective.

The author agrees with those opposed to placing the Mongoloid patient in an institution. Unless he has some serious associated handicap, there seems to be no reason why he should not be cared for at home, provided his environment is satisfactory. *Edward Solomons*

Journal of Pediatrics

Vol. 57, November, 1960.

*Fischer, A. E., and Moloshok, R. E.: Diabetic and Prediabetic Pregnancies With Special Reference to the Newborn, p. 704.

Fischer and Moloshok: Diabetic and Prediabetic Pregnancies With Special Reference to the Newborn, p. 704.

This paper analyzes the authors' experience with the infants born to 159 women, 97 of whom had clinical diabetes and 62 of whom had decreased tolerance to glucose. The maternal management of the diabetic mothers is given in general terms.

The 97 diabetic women were pregnant 177 times. The authors observed 124 of these pregnancies. Seventy-one of the 124 were terminated by cesarean section and 53 by vaginal delivery. There was a greater perinatal loss among those delivered vaginally. There was no significant difference in ratio of survival between the group with diabetes of less than 10 years' duration and that with diabetes of more than 10 years' duration.

Careful long-term medical and obstetric attention exert a favorable influence upon fetal survival. In the present series of 124 pregnancies among women with diabetes there was a total fetal loss of 23 per cent—a 16 per cent loss of viable infants and a neonatal loss of only 8 per cent. This is compared with the past pregnancy experience of this group of women under other auspices; of 53 pregnancies there was a total loss of 68 per cent, a loss of 53 per cent of viable fetuses and 35 per cent of live births.

Factors detrimental to the fetus of a diabetic mother are active in the 5 year period immediately before the onset of maternal diabetes but do not appear to operate earlier.

The management of infants born to diabetic mothers is described. It is emphasized that careful observation and good medical and nursery care are the most important factors favorably influencing survival. *J. Edward Hall*

New York State Journal of Medicine

Vol. 60, Nov. 15, 1960.

*Seneca, H., Latimer, J. K., and Zinsser, H.: Chemotherapy of Urinary Tract Infections, Past and Current, p. 3630.

Seneca, Latimer, and Zinsser: Chemotherapy of Urinary Tract Infections, p. 3630.

In the general approach to chemotherapy of urinary tract infections the essence of proper management is an accurate diagnosis. It is necessary to know the exact anatomic location of the lesion, the nature of the infecting pathogen, the source and route of infection, the duration of the infection, previous chemotherapy, and associated findings, such as obstruction or stricture. It is emphasized that in chronic, repeated, or recurrent infections through urologic, roentgenologic, and laboratory examinations are absolutely essential. The choice of the drug depends on the enzyme profile and the drug sensitivity pattern of the pathogen. A rather complete consideration concerning chemotherapy of specific bacterial infections is presented by the authors including species of Streptococcus, Pseudomonas, Aerobacter, Escherichia, Klebsiella, Alkaligenes, Proteus, and genitourinary tuberculosis infections. Side effects of drugs used in chemotherapy are discussed. *Reuben H. Adams*

Dec. 1, 1960.

*Landesman, R., and Knapp, R. C.: Diagnosis and Treatment of the Toxemias of Pregnancy. I. Diagnosis, p. 3830.

Landesman and Knapp: Diagnosis and Treatment of the Toxemias of Pregnancy. I. Diagnosis, p. 3830.

The authors report that periodic clinical examinations of all pregnant women have provided more accurate early diagnoses of toxemia. Improvements in diagnosis have made it possible to identify definite organic causes for certain categories of the syndrome that were formerly considered of unknown etiology. In addition to the working classification of the syndrome as defined by the American Committee on Maternal Welfare in 1952, an additional heading is suggested which would include toxemias related to or caused by some other disease unrelated to the pregnancy. Toxemias related to other organic diseases, as listed and discussed by the authors, are nephritis, pyelonephritis, congenital polycystic kidney disease, diabetes mellitus, coarctation of the aorta, pheochromocytoma, hyperfunction of the adrenal cortex, lupus erythematosus, and sickle cell disease. With the more extensive clinical classification of the varieties of toxemia, it is suggested that advantages may be achieved in management including determination of optimal time for delivery and methods of treatment. Also, more accurate predictions concerning recurrence of the toxemia and possible therapy in the interval between pregnancies for some conditions may be determined.

Reuben H. Adams

Dec. 15, 1960.

*Lipton, B., Gittler, R. D., and Slotnic, H. O.: Cardiovascular Effects of Oxytocin Injection (USP) Synthetic, Prepared Oxytocin, and the Ergot Alkaloids, p. 4006.

*Landesman, R., and Knapp, R. C.: Diagnosis and Treatment of the Toxemias of Pregnancy. II. Treatment, p. 4035.

Lipton, Gittler, and Slotnic: Cardiovascular Effects of Oxytocin Injection (USP) Synthetic, Prepared Oxytocin, and the Ergot Alkaloids, p. 4006.

The authors submit a preliminary report concerning a comparative study of the cardiovascular effects of prepared oxytocin, oxytocin injection (USP) synthetic, ergonovine maleate, and methyl ergonovine maleate in both anesthetized and unanesthetized subjects. One hundred anesthetized patients and 7 unanesthetized volunteers were included in this study. When administered intravenously in dilute infusions to anesthetized patients, prepared oxytocin (Pitocin) and oxytocin injection (USP) synthetic (Syntocinon) produced no cardiovascular changes, but in concentrated doses they produced hypotension. In unanesthetized subjects the same drugs administered intravenously in concentrated doses produced hypotension, tachycardia, and electrocardiographic changes. Ergonovine and methyl ergonovine, administered intravenously to anesthetized patients, produced no significant cardiovascular changes. The authors conclude that both prepared oxytocin and oxytocin injection (USP) synthetic when administered in a dilute intravenous infusion produce no significant cardiovascular changes. The potential hazard of shock occurring when prepared oxytocin is given because of the presence of vasopressin and animal protein is mentioned. However, it is stated that since the occurrence of shock during prepared oxytocin infusion is very rare it would require an extremely large series of cases studied over a long period of time to prove any clinical superiority of oxytocin injection (USP) synthetic as compared with prepared oxytocin.

Reuben H. Adams

Landesman and Knapp: Diagnosis and Treatment of the Toxemias of Pregnancy. II. Treatment, p. 4035.

A general review of treatment of the toxemias of pregnancy is presented. Through the establishment of special clinics for the care of toxemic patients the maternal risk has been reduced although high fetal losses persist because of the frequent early onset of the toxemic process and the complication of prematurity. Indications for bed rest, sedation, diuretics, anticonvulsant drugs, antihypertensive agents, and early delivery are considered. In severe preeclampsia and eclampsia the use of magnesium sulfate is discussed and its value as an anticonvulsant and its ease of administration are emphasized. A thorough dosage schedule to maintain a serum magnesium level near 7 mg. per milliliter is presented along with a discussion of signs which would interdict further maintenance doses. The use of antihypertensive agents with magnesium sulfate when there is danger of a cerebral vascular accident is pro-

posed and a combination of hydralazine hydrochloride (Apresoline) and cryptenamine (Unitensen) is presented as useful.

Reuben H. Adams

The Practitioner

Vol. 185, September, 1960.

*Hawkins, J.: Endometriosis, p. 265.

*Davidson, S.: Prolapse and Its Management, p. 271.

*Russell, C. S.: Malformations of the Female Genital Tract, p. 285.

*Rhodes, P.: Tuberculosis of the Genital Tract in Women, p. 290.

*Hamilton, J.: The Problem of Vaginitis, p. 296.

*Winterton, W. R.: The Etiology and Treatment of Amenorrhea, p. 301.

*deVere, R. E.: The Problem of Dysmenorrhea, p. 308.

Hawkins: Endometriosis, p. 265.

According to the author the four main sites of endometriosis are the uterus, ovary, rectosigmoid, and extrapelvic areas with laparotomy scars being the most important clinically. Experiments in Rhesus monkeys have proved that shed endometrium is viable and can implant.

The process of endometriosis is dependent upon ovarian function and regresses with the menopause. Pregnancy may also cause regression which is sometimes permanent, a fact that is of clinical import in the management of the younger woman who is desirous of further pregnancies. However, residual fibrosis, a sequela to the original lesion, will not regress with pregnancy or the menopause.

Widespread pelvic endometriosis may exist without symptoms. Half of those women with pelvic endometriosis have a distinctive type of dysmenorrhea which comes on prior to the period and persists throughout the menses. Sterility or relative infertility in the presence of demonstrable tubal patency may occur, as wall as menorrhagia and dyspareunia. Bladder or bowel involvement can closely mimic carcinoma as a result of fibrosis.

The treatment of endometriosis of the ovary is dependent on age, parity, desire for future pregnancy, and symptomatology. When conservation is not indicated, total abdominal hysterectomy along with bilateral salpingo-oophorectomy is the treatment of choice. Implants in the cul-de-sac usually regress. Methyltestosterone in doses of 5 to 10 mg. daily has certain limited use, and amelioration of the symptoms with this treatment supports the diagnosis. Radiotherapy has no place in the treatment of this condition.

Alexander H. Rosenthal

Davidson: Prolapse and Its Management, p. 271.

Obstetric trauma is the main predisposing factor to genital prolapse although prolapse is sometimes seen in the nullipara. Prolonged labor, precipitate delivery, hasty delivery with forceps, and poor pre- and postnatal care are predisposing factors.

Prolapse may be caused by changes in tissues brought about by estrogen withdrawal at the time of the menopause, stress factors such as sudden lifting, or conditions such as chronic bronchitis which are responsible for bouts of increased intra-abdominal pressure when coughing occurs. Symptoms vary from minimal discomfort to general lassitude, along with pelvic fullness or stress incontinence.

Prophylaxis includes good prenatal care, proper management of prolonged labor, the liberal use of the midline episiotomy, and postpartum rest. Vaginal wall prolapse seen in the postnatal period should be treated temporarily with a ring pessary and retroflexion of the uterus with a Hodge pessary. When definitive treatment for prolapse is indicated, the operation of choice is vaginal repair along with amputation of the cervix. In cases in which abdominal hysterectomy is indicated, vaginal plastic operations should precede the laparotomy. Preoperative topical estrogen is recommended for the postmenopausal patient.

The pessary is a poor substitute treatment and is reserved only for the seriously ill or for temporary use in the childbearing period. Vaginal plastic operations should be performed in the childbearing period only for severe symptoms. Subsequent pregnancies should then be terminated by cesarean section.

Alexander H. Rosenthal

Russell: Malformations of the Female Genital Tract, p. 285.

Malformations of the female genital tract are divided into defects due to failure of fusion or development of the Müllerian ducts, intersexuality, and developmental errors at the gonadal level. Defects resulting from failure of fusion of the Müllerian ducts vary from cases of a double vagina, uterus, and cervix to those of simply a bicornuate uterus. Failure of develop-

ment of the Müllerian ducts can occur on one or both sides, resulting in a rudimentary horn or total absence of the uterus. Such developmental failure can occur at the Müllerian or ovarian level, the latter being associated with lack of secondary sex characteristics.

Intersexuality refers to persons with varying degrees of ambisexual development. Female pseudohermaphroditism due to the adrenogenital syndrome is cited. This condition results from an overactive fetal adrenal gland which produces excessive androgen and causes an enlarged clitoris and varying degrees of fusion of the labial scrotal folds.

Developmental defects at the gonadal level are now better understood and are dependent on the chromosomal sex patterns. Cases of gonadal dysgenesis (Turner's syndrome) are due to nondisjunction of the sex chromosome pair resulting in an XO chromosome instead of an XX or XY chromosome.

Alexander H. Rosenthal

Rhodes: Tuberculosis of the Genital Tract in Women, p. 290.

Genital tuberculosis is usually secondary to infection elsewhere and should be regarded as a local manifestation of a generalized disease. The primary site is generally pulmonary with spread of the organism via the blood stream to the Fallopian tubes and then directly to the endometrium. Curettage may thus make the diagnosis. In a third of the cases there is spread to the ovaries. Peritoneal tuberculosis of childhood rarely spreads to the genitals.

A history of tuberculosis in a patient with gynecologic symptoms demands further investigation. In proved cases of genital tuberculosis 75 per cent have or have had tuberculosis in another site. Chest x-ray examination is indicated. No symptom is diagnostic, but vague pelvic discomfort, infertility, and changes from the individual's established menstrual pattern are common symptoms. Bimanual examination of the pelvis generally reveals no abnormality. Only rarely are the tubes definitely enlarged. Endometrium obtained by curettage should be subjected to microscopy examination, culture, and guinea pig inoculation. Culdoscopy and hysterosalpingography are sometimes helpful.

Treatment is by all three antituberculous drugs (streptomycin, PAS, and isoniazid) in varying combinations and given for at least a year. The efficacy of treatment may be judged by repeated examination and curettage. Surgical treatment is not often necessary but may have to be used for persistent pain or pelvic masses.

Alexander H. Rosenthal

Hamilton: Problem of Vaginitis, p. 296.

Adequate estrogen in the circulation helps to maintain a vaginal pH of 4.5 and the presence of Döderlein bacilli, and these act as the main defense against pyogenic organisms in the vagina. Because of the lack of estrogen in the childhood and postmenopausal periods, vaginitis in these age groups is often due to pyogenic infection.

In children the infecting organism is usually transmitted by utensils or clothes from infected adults. After identification of the organism, appropriate antibiotic treatment is given. In resistant cases the presence of foreign bodies should be suspected.

In the postmenopausal patient who has bloody discharge, diagnostic curettage should be performed to rule out endometrial carcinoma. Treatment consists of estrogens orally plus lactic acid suppositories or weak vinegar douches.

In the reproductive period the most common causes of vaginitis are infection with *Trichomonas vaginalis* or *Candida albicans*. Trichomonal vaginitis is thought to be largely venereal in origin. The diagnosis is made on the gross appearance of the discharge, microscopy examination of discharge suspended in saline, and culture of the organism. No one specific treatment has proved highly effective. Oral preparations have given poor results. Efforts to correct the pH with use of lactic acid suppositories or weak vinegar douches are helpful. Medicated suppositories, creams, and insufflations of various agents have all been used. Since menstrual discharge produces an alkaline pH, it is important to continue treatment during the flow.

Monilial vaginitis occurs with increased frequency during pregnancy and becomes less frequent after 50 years of age. It is now seen more commonly because of the widespread use of antibiotics. The diagnosis is made by the recognition of gram-positive fungi on smear examination and specific culture characteristics in Nickerson's medium. Treatment includes the daily painting of the vagina with aqueous gentian violet or insertion of vaginal tablets of nystatin.

Alexander H. Rosenthal

Winterton: Etiology and Treatment of Amenorrhea, p. 301.

Amenorrhea may be due to some dysfunction of the hypothalamic-pituitary-ovarian relationship. The differential diagnosis includes lesions at these various levels. Environmental changes, fear of pregnancy, and anxiety concerning fertility are psychic factors which can act on the hypothalamus and produce amenorrhea. Other endocrine factors such as thyroid and adrenal dysfunction and diabetes mellitus can also influence hormonal balance.

Investigation should include a complete history and physical examination plus the following investigations: (1) x-ray examination of the sella turcica, (2) urine examination for sugar, (3) BMR, (4) pelvic examination under anesthesia with sounding of the uterus, and (5) therapeutic test using 1 mg. stilbestrol three times a day for 21 days. Repetition of this course with the addition of progesterone, 10 mg. daily for 3 days, at the end of the series should result in withdrawal bleeding if the uterus is not the site of the causative lesion. Estimation of the urinary FSH and 17-ketosteroids may also help in the diagnosis.

Alexander H. Rosenthal

deVere: Problem of Dysmenorrhea, p. 308.

Primary dysmenorrhea is generally seen in patients with no underlying disease and is associated with ovulatory cycles. Pregnancy usually cures the disorder. Marriage may improve the condition, but occasionally this change in status results in ovulatory periods for the first time and resultant dysmenorrhea.

Dysmenorrhea is said to be caused by uterine ischemia along with increase in the strength of the uterine contraction during menses. Psychogenic factors are prominent in certain cases, and poor early sex education and guilt related to sexual function may be incriminated. Some sufferers are said to have a decreased pain threshold.

The treatment for mild cases includes analgesics with or without amphetamine and psychotherapy. A therapeutic test with the newer progesterones to stop ovulation can identify those with a very large psychological component, for they will not obtain relief with anovulatory bleeding. Curettage of the uterus is occasionally indicated after failure of more conservative measures. Presacral neurectomy should be limited to the severe resistant cases, with hysterectomy the last resort.

Alexander H. Rosenthal

Editorial

Vaccination against influenza in pregnancy

THE occurrence of three epidemic waves of influenza in the United States, two in the last quarter of 1957 and the first quarter of 1958 and a third in the early winter months of 1960, has served to recall to us the constant threat of widespread serious illness from this cause. Although the recent epidemics are far from the most serious that the United States has suffered in the memory of the present generation of physicians, nevertheless almost 60,000 excess deaths were recorded in the 6 months' period October, 1957, to March, 1958, and an excess of over 26,000 deaths in the 1960 epidemic. The 1957-1958 epidemic, world-wide in its distribution, was caused by a new antigenic variant of Type A influenza virus, subsequently termed Type A_2 or "Asian" influenza. This epidemic was associated, as is so often the case with influenza, with a marked excess mortality particularly among persons in the older age groups with chronic associated illness and among pregnant women.

Because of the concentration of mortality in these groups, the United States Public Health Service is urging a continuing program to protect these high-risk groups by annual vaccination. In several trials of the effect of vaccination it has been demonstrated that influenza vaccination may be expected to be 60 to 70 per cent effective in preventing the disease.

The dose for adults recommended by the Advisory Committee to the Surgeon General calls for an initial immunization of 1 c.c. (500 cca units) of polyvalent vaccine administered subcutaneously on two occasions separated by 2 or more months. Preferably, the first dose should be given no later than September 1 and the second no later than November 1. Persons previously immunized with polyvalent vaccine should be reinoculated with a single booster dose of 1 c.c. subcutaneously prior to November 1.

Although the ideal time for vaccination may be past for this year, the dates seem less essential with respect to the course of pregnancy than to the more constant problem of old age or chronic illness.

The appearance of an epidemic of influenza is scarcely predictable. It seems therefore wise that the advice of the Surgeon General be followed and that polyvalent vaccine be given to all pregnant women on the chance of the development of the epidemic or sporadic disease during the period of gestation.

A. B.
J. B.
H. T.

Correspondence

Pregnancy complicated by pyocolpos

To the Editors:

In the March issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY was published a letter from William Bickers, M.D., of the American University Hospital, Beirut, Lebanon, commenting on "pregnancy complicated by pyocolpos" and describing what he calls "salt packing" measures.

Dr. Bickers' letter is quite misleading and confusing in what concerns the localities where salt packing is practiced. From his letter the reader will conclude that Lebanon is a Bedouin country and that Lebanon and Saudi Arabia are, if not the same country, at least adjacent areas.

First of all we have no Bedouin in Lebanon which is quite far from Saudi Arabia. It takes more than one week by car to cover the distance between them, not to mention how long it takes by another way of traveling, if such a way ever existed. And being a Lebanese who lived in Lebanon up to a few years ago, I have never heard of anyone coming from Saudi Arabia to Lebanon on donkeys or camels. It would have been better and faster for a patient to go to a neighboring country like Iraq instead of Lebanon.

Second, and as Dr. Bickers knows quite well, Medicine and Obstetrics in Lebanon are quite advanced and modern and no one of us ever heard of the salt packing practice in the past or in the present.

If Dr. Bickers will take the time, I am sure he could still find a few retired old midwives high in the Lebanese mountains who will be glad to tell him that they never practiced salt packing or any other similar methods, especially since physicians were always available within short distances between any two villages or towns in Lebanon.

Antoine M. Harouny, M.D.

15008 Lorain Ave.
Cleveland 11, Ohio
March 20, 1961

Reply by Dr. Bickers

To the Editors:

Thank you for sending a copy of Dr. Harouny's patriotic defense of obstetric practice in Lebanon. Having been the guest of this beautiful country several times and having enjoyed the privilege of living and working among its hospitable people, I share his loyalty and devotion.

On Nov. 22, 1945, I operated in the American University Hospital upon the patient described in my letter (AM. J. OBST. & GYNEC. 81: 623, 1960). According to the history given by the husband, her first pregnancy had been normal. The second was complicated by postpartum hemorrhage and the vagina had been packed with salt. Upon examination, the upper third of the vagina was obliterated except for a small sinus tract. At operation the macerated fetus was removed from the left broad ligament, site of uterine rupture. This patient was from the Hijaz, brought to Acqaba by camel, thence by jeep to the American University of Beirut. Today she would go to the Khalid Idriss Hospital in Jeddah and receive expert attention.

In March of this year I examined in consultation a lady of high estate, not a Bedouin, who gave a history of 4 normal deliveries. In the last pregnancy, 4 years ago, the baby was unusually large and the patient suffered a "deep tear." This was treated by salt packing. Her complaint now is infertility. Upon examination the upper two thirds of the vagina was found to be replaced by scar tissue which made visualization of the cervix impossible.

I have never seen this condition in a Lebanese woman. We at the American University and our colleagues at the French Faculty are with Dr. Harouny in appreciation of high medical standards in Lebanon. Our students are coming more and more from neighboring countries so we can anticipate abandonment of salt packing everywhere in the near future.

William Bickers, M.D.

American University Hospital
Beirut, Lebanon
April 15, 1961

Nonsteroidal estrogen antagonist

To the Editors:

It has been brought to my attention that the animal work quoted in my article, "Observations on the Use of a Nonsteroidal Estrogen Antagonist" (Am. J. Obst. & Gynec. 81: 233, 1961), is not specific regarding authorship. All of this work was performed by Len Lerner with the assistance of F. J. Holthaus and C. R. Thompson. To be more specific, the last sentence in the third paragraph should preferably have read, "The findings of Lerner, Holthaus, and Thompson indicate that. . . ."

I regret not having referred to this excellent study more specifically.

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May 17, 1961

Postmenopausal bleeding

To the Editors:

In the April, 1961, issue of the American Journal of Obstetrics and Gynecology, Dr. Mackles and I reported a case of postmenopausal bleeding in which there was a negative diagnostic curettage but a positive endometrial cytosmear with use of the Clyman endometrial cannula. I would like to suggest that, in every case of recurrent postmenopausal uterine bleeding after a negative diagnostic curettage, an endometrial suction cytosmear be obtained immediately prior to the repeat curettage. In this manner it may be possible to pick up an early case of carcinoma of the Fallopian tube.

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April 24, 1961

Notice. *The Roster of American Obstetrical and Gynecological Societies, usually published in the January and July issues of the Journal, will henceforth appear only in January.*